Clinical trial results:
A phase II study of pazopanib in patients with metastatic or unresectable renal cell carcinoma (RCC) who have failed prior sunitinib therapy

Summary

EudraCT number	2010-022770-13
Trial protocol	IE SE
Global end of trial date	15 July 2020

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	ICORG 10-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01566747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	Ardilaun House, St Stephens Green, Ireland, D02 VN51
Public contact	Head of Clinical Operations, Cancer Trials Ireland, +353 16677211, regulatory@cancertrials.ie
Scientific contact	Head of Clinical Operations, Cancer Trials Ireland, +353 16677211, regulatory@cancertrials.ie

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	01 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2020
Global end of trial reached?	Yes
Global end of trial date	15 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to assess the progression free rate at 4 months (i.e. completion of 4 months of treatment, with no disease progression at 8 weeks, and no evidence to suggest disease progression before the 4 month time-point).

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations SI 190 of 2004 as amend and European Directive 2001/20/EC. The study was approved by the HPRA and Cork Teaching Hospitals Clinical Research Ethics Committee on 12th Jan 2011.

Background therapy:

N/A all patients will receive Pazopanib. Patient must have also received prior treatment with sunitinib for at least 12 weeks in order to participate in this study. Prior treatment with either temsirolimus or everolimus will also be allowed as these treatments have been proven to be effective as 2nd line therapy of RCC.

Evidence for comparator:

The aim of this study is to assess the efficacy of pazopanib in treating patients with metastatic renal cell carcinoma whose cancer has progressed following treatment with sunitinib. As there are currently a number of small molecules approved in the RCC setting, major interest now lies in defining the best sequence of drugs and whether persistent targeting of the VEGF receptor family is warranted following failure of a prior VEGF directed therapy. Sunitinib is a multi-kinase inhibitor of VEGFR 1, VEGFR 2, VEGFR 3, PDGFR α/β, c kit, Flt-3, CSF-1and RET while pazopanib is a selective inhibitor or VEGFR 1, 2, 3, PDGFR α/β and c kit. This study aims to assess if pazopanib retains activity against the RCC following progression on sunitinib therapy with the biological rationale being that the non-overlapping targets may confer different activity levels.

Actual start date of recruitment	08 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Ireland: 51
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	36
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

54 patients were consented from 8 sites in Ireland and Sweden from 08-Mar-2011 until 05-Feb-2016

Pre-assignment

Screening details:

The target population for this study was patients with metastatic or unresectable renal cell carcinoma, who had been previously treated with sunitinib and relapsed. The patients had to meet all other inclusion criteria and none of the exclusion criteria.

Period 1

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

Blinding implementation details:

N/A As Blinding Not Used for Study.

Arms

Arm title	Single Arm

Arm description:

Phase II single arm study of pazopanib after failure of 1st Line therapy with sunitinib in patietns with metastatic or unresectable RCC

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	GW786034
Other name	Votrient
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Pazopanib 800mg day to be given continuously until disease progression unacceptable toxicity or withdrawal of consent.
Pazopanib monohydrochloride is supplied as a series of aqueous film-coated tablets containing 200mg and 400mg of the freebase:
• 200mg, oval-shaped, white, packaged in bottles containing 34 tablets each
• 400mg, oval-shaped, white, packaged in bottles containing 68 tablets each
Starting on Day 1 of the Treatment Period, each subject will receive 800mg (2 X 400mg tablets) of pazopanib to be administered once daily by mouth. The 200mg tablets of pazopanib will be provided to subjects who need dose adjustments during the study
Response assessments were to be carried out every 8 weeks for the first 24 weeks (six months) and then every twelve weeks until disease progression. Safety assessments were to be carried out every 4 weeks for the first six months and then every eight weeks until disease progression.

Number of subjects in period 1	Single Arm
Started	54
Completed	4
Not completed	50
Adverse event, serious fatal	47
Consent withdrawn by subject	1

Study Closure	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Single Arm

Reporting group description: -

Reporting group values	Single Arm	Total	
Number of subjects	54	54	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	18	
From 65-84 years	36	36	
85 years and over	0	0	
Age continuous Units: years			
median	58.5		
full range (min-max)	40 to 81	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	41	41	
Race Units: Subjects			
Caucasian	54	54	
Height at creening (cm) Units: cm			
median	174		
full range (min-max)	148 to 194	-	
Weight at Screening Units: kg			
median	79.8		
full range (min-max)	46.6 to 138.2	-	

Subject analysis sets

Subject analysis set title	Analysis Arm
Subject analysis set type	Full analysis

Subject analysis set description:

As this is a single arm study, an extra arm is required to be added so that the statistical analysis can be added. This is NOT extra information or an extra arm. There is only one arm for this study. There were only 54 subjects analysed in total

Reporting group values	Analysis Arm		
Number of subjects	54		
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)	18		
From 65-84 years	36		
85 years and over	0		
Age continuous Units: years			
median			
full range (min-max)			
Gender categorical Units: Subjects			
Female			
Male			
Race Units: Subjects			
Caucasian			
Height at creening (cm) Units: cm			
median			
full range (min-max)			
Weight at Screening Units: kg			
median			
full range (min-max)			

End points

End points reporting groups

Reporting group title	Single Arm

Reporting group description:

Phase II single arm study of pazopanib after failure of 1st Line therapy with sunitinib in patietns with metastatic or unresectable RCC

Subject analysis set title	Analysis Arm
Subject analysis set type	Full analysis

Subject analysis set description:

As this is a single arm study, an extra arm is required to be added so that the statistical analysis can be added. This is NOT extra information or an extra arm. There is only one arm for this study. There were only 54 subjects analysed in total

Primary: Progression Free Rate at 4 Months

End point title	Progression Free Rate at 4 Months

End point description:

Progression Free-Rate at 4 monts (i.e. completion of 4 months of treatment, with no disease progression at 8 weeks, and no evidence to suggest progression before the 4-month time-point). The PFS Rate was 23 Patients of 46 evaluable patients (50%) with a 955 CI. Simon's two-stage design required 25 of a planned 43 evaluable patients (50%) with a 95% CI. Simon's two-stage design requires 25 of a planned 43 evaluable patients to be progression free at 4-months in order to reject a PFS rate of 45%, so this unacceptable rate cannot be rejected.
Progression Free = Complete Response (0 Patients) + Partial Response (7 Patients) + Stable Disease (16 Patients).
As a check on robustness, the analysis was repeated for the Safety Set (all available data for the primary endpoint). The PFS rate was 24 patients of 48 patients (50.0%), with a 95% CI of [36.4 – 63.6]. This PFS rate also means that an unacceptable rate of 45% cannot be rejected.

End point type	Primary

End point timeframe:

From Time of Treatment Start Until 4 Months After Treatment start

End point values	Single Arm	Analysis Arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	46	46[1]		
Units: Patients				
number (confidence interval 95%)				
Progresssion Free Rate at 4 Months	50 (36.1 to 63.9)	50 (36.1 to 63.9)		

Notes:

[1] - The statistical arm is being used as it is a single arm study. Only 46 subjects were analysed total

Statistical analyses

Statistical analysis title	Progression-free survival rate at 4 months

Statistical analysis description:

Progression-free survival rate

Comparison groups	Single Arm v Analysis Arm

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[2]
Method	PFS Rate & CI
Parameter estimate	Progression-free survival rate
Point estimate	50
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.1
upper limit	63.9

Notes:

[2] - Progression-free survival rate and confidence interval

Secondary: Median Time to Progression Free Survival (PFS)

End point title	Median Time to Progression Free Survival (PFS)

End point description:

Progression-free survival, defined as the length of time between the date of starting treatment and the earliest date of disease progression or death due to any cause. A total of 43 Patients (out of 48 - 89.6%) progressed on study treatment including 3 patients who discontinued study treatment for reason of clinical progression.

End point type	Secondary

End point timeframe:

Date of Starting Treatment and earliest date of disease progression or death due to any cause

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Months				
number (confidence interval 95%)				
Median Time to Progression	4.76 (3.68 to 5.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)

End point description:

Overall response rate (ORR), defined as the percentage of patients who achieved at least a partial response. It is Patients who had complete response + Partial Response.

End point type	Secondary

End point timeframe:

From start of study treatment until partial/complete response

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Patients				
number (confidence interval 95%)				
Best Response During Study Treatment	22.9 (13.3 to 36.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival, defined as the length of time between the date of starting treatment and the date of death due to any cause. A total of 47 deaths (87.0%) were reported during the study, with median overall survival time of 19.1 months and an accompanying 95% CI of [10.5 – 26.5].
Cause of death was disease progression in all cases except for one patient whose cause of death was an AE related to a new anti-cancer treatment for disease progression.

End point type	Secondary

End point timeframe:

Date of starting treatment and the date of death due to any cause

End point values	Single Arm			
Subject group type	Reporting group			
Number of subjects analysed	47[3]			
Units: Months				
number (confidence interval 95%)				
Median Time to Death	19.1 (10.5 to 26.5)			

Notes:

[3] - 47 deaths were reported

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs meeting serious criteria were reported up to 30 days after last dose of IMP. AEs or SAEs after 30 days of active follow up deemed to be causally related to IMP during study was forwarded to CTI

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Single Arm

Reporting group description:

Phase II single arm study of pazopanib after failure of 1st Line therapy with sunitinib

Serious adverse events	Single Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 54 (29.63%)		
number of deaths (all causes)	47		
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominial Pain Upper			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vomiting			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Back Pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mobility decreased			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsilitis			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Single Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 54 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pain in lumps in neck and back (soft tissue metastases)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
New lt buttock lump soft tissue metastasis/nodule)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vascular disorders			
Increase tsh			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	24 / 54 (44.44%)		
occurrences (all)	34		
Hypotension			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	7		
Surgical and medical procedures			
Dental extraction gum			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

Tooth removed subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Dental extraction subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2		
Spinal fusion surgery subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Shoulder replacement subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
General disorders and administration site conditions Malignant pyrexia subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Fatigue subjects affected / exposed occurrences (all)	29 / 54 (53.70%) 41		
Lump in right forearm appears larger subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Tenderness in both feet subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Bilateral leg oedema scattered subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Pyrexia subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 4		
Feeling cold subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		
Swelling rt groin			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pitting oedema			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Left sided pain radiating to back			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Flu like symptoms			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Bipedal oedema			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
chest pain			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Left calf swelling			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Inflammation of left arm post aredia iv			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Mucositis			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	6		
Pain			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	4		
Malaise			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Reproductive system and breast disorders			

Blood discharge from penis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Swollen penis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Testicular pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Intermittant scrotal rash			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Crepes left upper lobe			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Sore throat			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Cough			
subjects affected / exposed	8 / 54 (14.81%)		
occurrences (all)	11		
Post nasal drip			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Sob on exertion			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Runny nose			

subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Shortness of breath on exertion				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Dyspnoea				
subjects affected / exposed	6 / 54 (11.11%)			
occurrences (all)	7			
Bronchopulmonary hemorrhage				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Wheezes/crackles in right lower base lung				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Pneumonitis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Haemoptysis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Pleural effusion				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Lung infection				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	2			
Bilateral pulmonary embolism				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	3			
Pleuretic chest pain				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Hoarse voice				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			

Blocked nose			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Confusion			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Low mood			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hallucinations			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Investigations			
Weight Loss			
subjects affected / exposed	9 / 54 (16.67%)		
occurrences (all)	19		
hypokalemia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	3		
Raised bilirubin			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Raised upc			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Increase in bp			

subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Alkaline phosphatase increase				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	4			
Raised alt				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	3			
Weight gain				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	2			
Raised creatinine				
subjects affected / exposed	9 / 54 (16.67%)			
occurrences (all)	17			
Ldh increase				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Glucose increase				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	3			
Albumin decrease				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	2			
Phosphate decrease				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	3			
Rising grade 3 gamma gt				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Decreased magnesium				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Decreased neutrophilis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Platlets decrease				

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Sodium increase			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Raised crp			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pleurisy			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Alt increase			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hypophosphatemia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Abnormal ecg			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Pseudoaneurysm			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Wound bleeding lesion left ring finger			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Right leg pain post op			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Incisional hernia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain (hernia repair site			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	2		
Congenital, familial and genetic disorders			
Incidental finding of pfo			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Bradycardia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Asymptomatic lvef			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Nervous system disorders			
Headaches			
subjects affected / exposed	17 / 54 (31.48%)		
occurrences (all)	20		
Light headedness			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Taste disturbance			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Peripheral neuropathy intermittent			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Memory impairment			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Burning sensation feet			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	5		
Sensory neuropathy (fingers)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Spinal cord compression			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vasovagal event			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Restless leg syndrome			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Worsening anemia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	8		
Iliac limphadenopathy			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Hearing loss			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Right ear pain			

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Ear disorder			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Eye disorders			
Watery eyes			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vitreous hemorrages			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Cyst eye			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain in right eye secondary to shingles			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Vision disturbance (flashing)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Mild periorbital oedema			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Visual disturbance			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal cramps			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	8		
Heartburn			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Pain in right side abdomen			

subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	24 / 54 (44.44%)			
occurrences (all)	74			
Abdominal pain				
subjects affected / exposed	10 / 54 (18.52%)			
occurrences (all)	11			
Abdominal discomfort				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	3			
Tender abdomen				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	15 / 54 (27.78%)			
occurrences (all)	22			
Ruq tendernes				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	17 / 54 (31.48%)			
occurrences (all)	29			
Gastric reflux				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Vomiting				
subjects affected / exposed	13 / 54 (24.07%)			
occurrences (all)	19			
Abdominal bloating				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Dyspepsia				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Dry mouth				

subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	3			
Flatulance				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Pancreatitis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Pain abdomen				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Abdominal soreness (gastric pain)				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Gastritis				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Esophagitis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Haemorrhoids				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Palpation soreness epigastric				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Belching				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Sore on lips				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Tongue sensitivity				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Sluggish bowel				

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Discomfort right upper quadrant			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	3		
Pain ruq			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Gastroesophageal reflux			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		
Anal pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Stomach rumbling			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Upset stomach			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Cholelithiasis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin discolouration nipple area			

subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Hair colour change				
subjects affected / exposed	9 / 54 (16.67%)			
occurrences (all)	9			
Small erythrematous lesions				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Dry skin on face				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Dry skin on hands				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Yellow discolouration of skin				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Alopecia				
subjects affected / exposed	5 / 54 (9.26%)			
occurrences (all)	5			
Dry skin on feet				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Painful callus r foot				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Hfsr				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Palm rash				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Skin rash allergy				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Urticaria skin rash bilateral arms and				

legs				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Urticaria to bilateral arms and 2 [degree] to bites				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Rash with itch				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	2			
Skin rash				
subjects affected / exposed	7 / 54 (12.96%)			
occurrences (all)	8			
Worsening rash (likely cutaneous lupus)				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Dry skin				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Scalp rash				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Plantar palmar syndrome				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	6			
Skin change				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Facial Rash				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	2			
Hyperkeratosis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Skin lesion behind (l) ear lobe				

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Seborrheic dermatitis - face			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Ecchymosis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Skin changes-facial redness			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Renal and urinary disorders			
Increase in urine output			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Urinary frequence increase			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Urinary urgency			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Proteinurea			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	3		
Urine discoloration			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Urine disorders (bilirubin ++)			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	14 / 54 (25.93%)		
occurrences (all)	18		
Ankle Swelling			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Calf cramp			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain right foot			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain right pelvis +leg			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Arthralgia right hip			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
General weakness in leg			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Shoulder pain			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	8		
Reduced mobility			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Painful r foot			

subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Painful lump in inner groin				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Leg & feet cramps intermittent				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Leg cramps				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
groin pain				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	3			
Lower limb pain at night				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Arthralgia				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	3			
Pain jaw				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	3			
Pain lower limb				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Pain lower back				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	3			
Pain to r heel				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Back ache				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Ganglion left wrist				

subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Lesion to forehead worsening. lytic lesion (skull)				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Left groin discomfort				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
hip pain				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	4			
Myalgia				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	3			
Red tender sides of feet				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Lower rib pain				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Rt axilla pain				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	2			
Rt scapular pain				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	2			
Osteonecrosis of the jaw				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Pain left knee				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Supraspinatus tendonitis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			

groin tenderness				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	2			
General joint stiffness				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Sore right foot				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Sore toe				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Pain in upper right arm				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Infections and infestations				
Oral thrush				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Chest infection				
subjects affected / exposed	5 / 54 (9.26%)			
occurrences (all)	6			
Head cold				
subjects affected / exposed	4 / 54 (7.41%)			
occurrences (all)	4			
Lrti (slight wheese + Cough				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Nasal candidiasis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Oropharyngeal candidiasis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Candidiasis r axilla				

subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Urinary tract infection				
subjects affected / exposed	4 / 54 (7.41%)			
occurrences (all)	4			
Flu				
subjects affected / exposed	2 / 54 (3.70%)			
occurrences (all)	2			
Viral cold				
subjects affected / exposed	3 / 54 (5.56%)			
occurrences (all)	3			
Buttock abscess				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Glass density in both lungs				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Cutaneous fungal infection				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Shingles				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Leg ulcer infectionLeg ulcer infection				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Cystitis				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Rti respiratory tract infection				
subjects affected / exposed	6 / 54 (11.11%)			
occurrences (all)	6			
Cold sore				
subjects affected / exposed	1 / 54 (1.85%)			
occurrences (all)	1			
Bronchitis				

subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Left basal pneumonia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Infected right tonsil			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	8 / 54 (14.81%)		
occurrences (all)	13		
Hyponatremia			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Cachectic			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Pain rt shoulder			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Appetite decrease			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	5		
Hyperphosphatemia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Hypermagnesemia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	2 / 54 (3.70%)		
occurrences (all)	2		

Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 2		
Hyperkalemia subjects affected / exposed occurrences (all)	2 / 54 (3.70%) 2		
Diabetes worsened subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2011	Original Approved Protocol was Protocol V1.0 04Oct2010. It was updated to Protocol V2.0 02Feb2011, but these were non substantial amendments (to edit Data Management procedures for the study including change of group statistician details & some admin changes). This update was submitted with the amendment for Protocol V3.0 21 June 2011. Protocol V3.0 was updated for a number of reasons including to correct requirements for BP levels, changes to Inclusion/Exclusion Criteria/addition of PI at site & removal of a site, Inclusion of planned analysis for the secondary efficacy endpoints, admin changes. Protocol V3.0 was not approved by the Irish Reg Authorities as they requested that a sentence needed to be added regarding Inclusion Criteria after the text on Sunitinib toxicity and eligibility - 'The Investigator should be aware of the patient's Intolerance/Toxicity with prior sunitinib treatment and take this into account when assessing eligibility'. This update resulted in Protocol V4.0 13-Sept-2011 which was approved.
08 October 2013	Protocol Version 5.0 11-Mar-2013: Principal Changes are: - Requirement for an extra safety visit to assess liver function at week 6 added in response to updated safety info for pazopanib issued via Dear Investigator Letter. - Change in frequency of CT scans after the 24 week time-point to every 12 weeks (from every 8 weeks) which is in line with Standard of Care - Clarification that Dose Modifications for the managing of treatment related AEs are mandatory as opposed to recommended. -Added recommendations on the use medications that increase gastric pH (PPIs and H2-receptor antagonists) asper IB V10 - Clarification in the working of primary & secondary endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported