Clinical trial results:
A Phase II Study of GW786034 Using a Randomized Discontinuation Design in Subjects with Locally Recurrent or Metastatic Clear-Cell Renal Cell Carcinoma

Summary

EudraCT number	2005-002212-13
Trial protocol	GB CZ BE
Global end of trial date	10 September 2013

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	15 March 2015

Trial information

Trial identification

Sponsor protocol code	VEG102616

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	13 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal objective of the trial is to compare the progressive disease rate at 16 weeks post-randomization of subjects receiving GW786034 or placebo and to determine the stable disease rate at 12 weeks in the Lead-in phase.

Protection of trial subjects:

An Independent Data Monitoring Committee was formed to evaluate periodic safety and efficacy data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 October 2005
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	Australia: 49
Country: Number of subjects enrolled	China: 13
Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Malaysia: 13
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	United States: 63
Country: Number of subjects enrolled	Belgium: 45
Country: Number of subjects enrolled	Czech Republic: 15
Worldwide total number of subjects	225
EEA total number of subjects	60

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)	150
From 65 to 84 years	75
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was originally designed as a Phase II, multi-centre study utilizing a randomized discontinuation design. In the original study design, a 12-week Lead-in Phase was an open-label period during which all enrolled participants received pazopanib.

Pre-assignment

Screening details:

All participants began with 12 weeks of open-label treatment. In the original design, participants with stable disease at Week 12 were to be randomized. After the interim analysis, the study was amended to be treated like a single-arm open-label study. Any participants who had been randomized to placebo were to be crossed back to pazopanib.

Period 1

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

Arms

Arm title	Pazopanib 800 mg

Arm description:

Pazopanib 800 milligrams (mg) (tablets) administered orally once a day.

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:

- pazopanib (GW786034) tablets were administered orally, once daily
- participants fasted for at least 2 hours prior to dosing and at least 1 hour post-dose, with the exception of water which was allowed freely
- the dose reduction (to 600 mg or 400 mg) due to safety reason was allowed as well as dose escalation to 800 mg when clinically appropriate

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

- placebo tablets were administered orally, once daily
- participants fasted for at least 2 hours prior to dosing and at least 1 hour post-dose, with the exception of water which was allowed freely

Number of subjects in period 1	Pazopanib 800 mg
Started	225
Completed	129
Not completed	96
Adverse event, serious fatal	7
Sponsor Terminated Study	2
Participant was Hospitalized until Death	1
Off Study Medication for >21 Days	1
Developed Secondary Malignancy	1
Disease Progression	13
Consent withdrawn by subject	12
Adverse event, non-fatal	30
Death	1
Declining Performance Status	1
Primary Investigator Discretion	2
Lost to follow-up	23
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Pazopanib 800 mg
Reporting group description:	
Pazopanib 800 milligrams (mg) (tablets) administered orally once a day.	

Reporting group values	Pazopanib 800 mg	Total	
Number of subjects	225	225	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.8		
standard deviation	± 10.33	-	
Gender categorical Units: Subjects			
Female	69	69	
Male	156	156	
Race Units: Subjects			
White	178	178	
Asian-Japanese/East Asian/South East Asian HER	38	38	
African American/African Heritage (HER)	4	4	
Asian-Central/South Asian Heritage	2	2	
American Indian or Alaska Native and White	1	1	
Asian-Mixed Asian Heritage	1	1	
Native Hawaiian or other Pacific Islander	1	1	

End points

End points reporting groups

Reporting group title	Pazopanib 800 mg

Reporting group description:

Pazopanib 800 milligrams (mg) (tablets) administered orally once a day.

Primary: Overall Response by RECIST criteria in Participants

End point title	Overall Response by RECIST criteria in Participants[1]

End point description:

The overall response is the number of participants who experience a confirmed complete (CR) or partial response (PR) of the total analysis population. Per the Response Evaluation Criteria In Solid Tumors (RECIST): CR = all detectable tumor has disappeared, PR = a >=30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum, Progressive disease (PD) = a >=20% increase in target lesions, Stable Disease = small changes that do not meet previously given criteria. Overall Response: Estimated value = 34.7%, 2-sided 95% CI=28.4% to 40.9%. Estimation Parameter: Percentage. The estimated value provided is the response rate.

End point type	Primary

End point timeframe:

Baseline to Response (up to 2.40 years). Assessments occurred at Week 12 and every 8 weeks thereafter

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: Statistical information is entered in the endpoint description. The system does not allow statistical data to be entered in the statisticial analysis section for studies with 1 treatment arm.

End point values	Pazopanib 800 mg			
Subject group type	Reporting group			
Number of subjects analysed	225[2]			
Units: Participants				
Complete Response	3			
Partial Response	75			
Stable Disease	101			
Progressive Disease	24			
Not evaluable	22			
Complete Response + Partial Response	78			

Notes:

[2] - All Enrolled Population: all participants who received at least one dose of pazopanib

Statistical analyses

No statistical analyses for this end point

Primary: Stable disease at 12 weeks - Interim Analysis of first 60 participants

End point title	Stable disease at 12 weeks - Interim Analysis of first 60 participants[3]

End point description:

The protocol called for an interim analysis of the first 60 participants to determine their status at Week 12, and to determine the number of participants with stable disease, although all categories were reported. Stable disease is defined as a disease that has not grown enough to be called progressive

disease and has not shrunk enough to be called partial/complete response. Estimated value = 42%, 2-sided 95% CI=29% to 54%. Estimation Parameter: Percentage. The estimated value is the percentage of the first 60 participants who had stable disease at Week 12, as assessed by the investigator.

End point type	Primary

End point timeframe:

Week 12

Notes:

[3] - 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: Statistical information is entered in the endpoint description. The system does not allow statistical data to be entered in the statistical analysis section for studies with 1 treatment arm.

End point values	Pazopanib 800 mg			
Subject group type	Reporting group			
Number of subjects analysed	60[4]			
Units: Participants				
Complete Response	0			
Partial Response	23			
Stable Disease	25			
Progressive Disease	3			

Notes:

[4] - Subset of the All Enrolled Population including only the first 60 participants

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Using RECIST criteria: date of first confirmed tumor response (CR or PR) to date of tumor progression or to death. Participants who did not progress or die were censored at their last radiologic assessment. Only participants who had a response were analyzed. The upper limit of the 95% confidence interval could not be determined (not reached) because too few responses with a known end date; therefore, the value of 99999 was entered which represents NA.

End point type	Secondary

End point timeframe:

First response until progression of disease (up to 2.40 years). Assessments occurred at Week 12 and every 8 weeks thereafter

End point values	Pazopanib 800 mg			
Subject group type	Reporting group			
Number of subjects analysed	78[5]			
Units: weeks				
median (confidence interval 95%)	68 (53.7 to 99999)			

Notes:

[5] - All Enrolled Population that had a CR or PR.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free Survival is defined as the interval between the first day of treatment and the earliest date of disease progression or death due to any cause, whichever occurred first. Progressive disease is defined as a >=20% increase in target lesions. Participants who did not progress or die were censored at their last radiologic assessment.

End point type	Secondary

End point timeframe:

From the first day of treatment to the earliest date of disease progression or death due to any cause (up to 2.40 years)

End point values	Pazopanib 800 mg			
Subject group type	Reporting group			
Number of subjects analysed	225[6]			
Units: weeks				
median (confidence interval 95%)	45.3 (36 to 59.1)			

Notes:

[6] - All Enrolled Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Until participant was off study, approximately 7.84 years	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Pazopanib 800 mg
Reporting group description:	
Pazopanib 800 mg (tablets) administered orally once a day.	

Serious adverse events	Pazopanib 800 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 225 (35.56%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemangioblastoma			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hypertension			
subjects affected / exposed	2 / 225 (0.89%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 225 (1.78%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	2 / 225 (0.89%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Oedema peripheral			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	3 / 225 (1.33%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	1 / 2			
Haemoptysis				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	6 / 225 (2.67%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	2 / 225 (0.89%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	5 / 225 (2.22%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	2 / 225 (0.89%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	3 / 225 (1.33%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase				

increased				
subjects affected / exposed	2 / 225 (0.89%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood thyroid stimulating hormone decreased				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood urea increased				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Body temperature increased				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	3 / 225 (1.33%)			
occurrences causally related to treatment / all	5 / 6			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural				

complications				
Femur fracture				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Stab wound				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural complication				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postoperative wound complication				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Hydrocele				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				

subjects affected / exposed	2 / 225 (0.89%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	2 / 225 (0.89%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Stress cardiomyopathy				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				

subjects affected / exposed	2 / 225 (0.89%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nerve root compression				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Eye disorders				
Retinal tear				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	3 / 225 (1.33%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Ascites				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 225 (0.89%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	3 / 225 (1.33%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Ileal perforation				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal ulcer				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	2 / 225 (0.89%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Oesophagitis				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				

subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 225 (0.89%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhoidal haemorrhage				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal stenosis				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				

subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Jaundice				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bile duct stenosis				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Skin lesion				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proteinuria				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Urogenital haemorrhage				

subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	2 / 225 (0.89%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Lower respiratory tract infection				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anal abscess				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	3 / 225 (1.33%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	1 / 225 (0.44%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	2 / 225 (0.89%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				

subjects affected / exposed	1 / 225 (0.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pazopanib 800 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	215 / 225 (95.56%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	32 / 225 (14.22%)		
occurrences (all)	79		
Aspartate aminotransferase increased			
subjects affected / exposed	28 / 225 (12.44%)		
occurrences (all)	61		
Weight decreased			
subjects affected / exposed	24 / 225 (10.67%)		
occurrences (all)	42		
Vascular disorders			
Hypertension			
subjects affected / exposed	100 / 225 (44.44%)		
occurrences (all)	133		
Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 225 (13.78%)		
occurrences (all)	42		
Dysgeusia			
subjects affected / exposed	57 / 225 (25.33%)		
occurrences (all)	63		
Headache			
subjects affected / exposed	47 / 225 (20.89%)		
occurrences (all)	68		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	13 / 225 (5.78%)		
occurrences (all)	15		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 225 (6.22%)		
occurrences (all)	15		
Chest pain			
subjects affected / exposed	16 / 225 (7.11%)		
occurrences (all)	18		
Fatigue			
subjects affected / exposed	108 / 225 (48.00%)		
occurrences (all)	150		
Mucosal inflammation			
subjects affected / exposed	12 / 225 (5.33%)		
occurrences (all)	14		
Oedema peripheral			
subjects affected / exposed	20 / 225 (8.89%)		
occurrences (all)	23		
Pyrexia			
subjects affected / exposed	16 / 225 (7.11%)		
occurrences (all)	19		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	12 / 225 (5.33%)		
occurrences (all)	13		
Abdominal pain			
subjects affected / exposed	41 / 225 (18.22%)		
occurrences (all)	52		
Abdominal pain upper			
subjects affected / exposed	13 / 225 (5.78%)		
occurrences (all)	14		
Constipation			
subjects affected / exposed	39 / 225 (17.33%)		
occurrences (all)	45		
Diarrhoea			

subjects affected / exposed	148 / 225 (65.78%)		
occurrences (all)	305		
Dyspepsia			
subjects affected / exposed	25 / 225 (11.11%)		
occurrences (all)	31		
Flatulence			
subjects affected / exposed	14 / 225 (6.22%)		
occurrences (all)	17		
Nausea			
subjects affected / exposed	100 / 225 (44.44%)		
occurrences (all)	146		
Stomatitis			
subjects affected / exposed	13 / 225 (5.78%)		
occurrences (all)	14		
Vomiting			
subjects affected / exposed	52 / 225 (23.11%)		
occurrences (all)	88		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	44 / 225 (19.56%)		
occurrences (all)	60		
Dysphonia			
subjects affected / exposed	12 / 225 (5.33%)		
occurrences (all)	16		
Dyspnoea			
subjects affected / exposed	26 / 225 (11.56%)		
occurrences (all)	29		
Epistaxis			
subjects affected / exposed	25 / 225 (11.11%)		
occurrences (all)	32		
Oropharyngeal pain			
subjects affected / exposed	15 / 225 (6.67%)		
occurrences (all)	20		
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	26 / 225 (11.56%) 27		
Dry skin subjects affected / exposed occurrences (all)	14 / 225 (6.22%) 16		
Erythema subjects affected / exposed occurrences (all)	12 / 225 (5.33%) 13		
Hair colour changes subjects affected / exposed occurrences (all)	100 / 225 (44.44%) 108		
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	25 / 225 (11.11%) 42		
Rash subjects affected / exposed occurrences (all)	37 / 225 (16.44%) 72		
Skin hypopigmentation subjects affected / exposed occurrences (all)	14 / 225 (6.22%) 14		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	13 / 225 (5.78%) 15		
Insomnia subjects affected / exposed occurrences (all)	21 / 225 (9.33%) 27		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	36 / 225 (16.00%) 50		
Back pain subjects affected / exposed occurrences (all)	29 / 225 (12.89%) 36		
Muscle spasms			

subjects affected / exposed	20 / 225 (8.89%)		
occurrences (all)	30		
Myalgia			
subjects affected / exposed	12 / 225 (5.33%)		
occurrences (all)	12		
Pain in extremity			
subjects affected / exposed	20 / 225 (8.89%)		
occurrences (all)	36		
Musculoskeletal chest pain			
subjects affected / exposed	12 / 225 (5.33%)		
occurrences (all)	13		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 225 (8.00%)		
occurrences (all)	23		
Upper respiratory tract infection			
subjects affected / exposed	22 / 225 (9.78%)		
occurrences (all)	31		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	70 / 225 (31.11%)		
occurrences (all)	86		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2006	-Updated sponsor information and added EUDRA No. -The randomized portion of the trial was stopped and all subjects had to receive GW786034. The objectives and data analysis were clarified to define the response rate calculation -Updated new treatment approvals -Included birth control requirements for males in inclusion/exclusion criteria -Clarified upper limit of allowed warfarin dosing -Urine serum pregnancy testing was allowed on Day 1. Added assessments for albumin, inorganic phosphate and magnesium. Subjects had free T3 and T4 assessment if TSH was abnormal. Clarified timing of visit windows, screening period events and the continuation visit phase events -Bone scan was planned to be obtained for all subjects at baseline. If the baseline scan was positive, a repeat scan had to be obtained at the time of the confirmation of a CR or PR. If the scan was negative, a repeat scan was not required. The scans at week 12 and 24 were removed. The scans were allowed at any time if clinically indicated -The first disease assessment in the Treatment Phase was planned to be done at week 8 and per time and event schedule. A confirmation of a CR or PR was planned to be conducted at a minimum interval of 4 weeks from the scan that initially revealed the CR or PR. The "clock" was reset for subsequent scans which were obtained approximately 8 weeks after the confirmation scan. Disease assessment of brain, thorax, abdomen and pelvis using imaging studies were planned to be obtained at screening and two-part disease assessment of thorax, abdomen and pelvis were planned to be obtained during the treatment periods unless clinically indicated. -Clarified sections 8.1-8.2 regarding concomitant medications for verapamil, pimozide, propafenone and diltiazem. Prohibited erectile dysfunction medications -Clarified disease related outcomes or events reporting -The study included IDMC -Study assessments aligned with the time event schedule -End of randomization clarified in schema
25 August 2009	Change 1 – Sponsor information: Updated with new medical monitoring information Change 2 – Visit assessment schedule: Allow subject visits from every 4 weeks to visit every 12 weeks after week 148. Change 3 – Time and events table for visit after week 148: insert new table to address details of the visits after week 148. Change 4 – Investigational Product: Allow subject in the future to transition from 100mg and 500mg tablets to 200mg and/or 400mg tablets.
19 August 2011	Change 1 – Remove old information: This amendment permits continued access to clinical trial material for subjects ongoing at the time of implementation of this amendment with adjustment to the frequency of clinical visits, scans and labs. Patient treatment and disease management will be at the discretion of the treating physician and as indicated by local standard of medical care of local standard of medical care and local approved labeling (or the DCSI). Change 2 – Data Collection: Investigators will only be required to collect and report to the Sponsor SAEs, pregnancies and non-serious AEs leading to IP discontinuation, other reasons leading to IP withdrawal and any non-serious AEs the investigator deems important to report using the forms provided. Collection of additional safety information will no longer be required by the Sponsor but will be at the discretion and judgment of the investigator. Change 3 – Sponsor information: Updated with new medical monitor information.

16 November 2011	This amendment changes the description of the investigational product GW786034 to: pazopanib monohydrochloride salt is supplied as aqueous film-coated tablets containing either 200mg or 400mg of the free base. Both the 200mg and the 400mg tablets are oval shaped and white in color. Refer to the pazopanib IB for information regarding the physical and chemical properties of pazopanib and a list of excipients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported