Clinical trial results:
PRINCIPAL: A Prospective Observational Study of Real World Treatment Patterns and Treatment Outcomes in Patients with Advanced or Metastatic Renal Cell Carcinoma Receiving Pazopanib

Summary

EudraCT number	2011-003065-15
Trial protocol	FI
Global end of trial date	29 December 2014

Results information

Result version number	v1 (current)
This version publication date	20 August 2020
First version publication date	20 August 2020

Trial information

Trial identification

Sponsor protocol code	VEG115232

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 ,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 ,

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	29 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of the PRINICIPAL study was to evaluate the real world effectiveness and safety of pazopanib in patients with advanced and/or metastatic RCC.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 July 2012
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	Finland: 14
Country: Number of subjects enrolled	Argentina: 22
Country: Number of subjects enrolled	Austria: 30
Country: Number of subjects enrolled	Belgium: 53
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	Estonia: 18
Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	Greece: 48
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Italy: 91
Country: Number of subjects enrolled	Lebanon: 2
Country: Number of subjects enrolled	Spain: 150
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Turkey: 19
Country: Number of subjects enrolled	United Kingdom: 65
Country: Number of subjects enrolled	United States: 64
Worldwide total number of subjects	657
EEA total number of subjects	528

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)	281
From 65 to 84 years	360
85 years and over	16

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This was a global, multi-centre, long-term, prospective, observational study to evaluate treatment patterns and clinical outcomes in patients with advanced or metastatic clear cell, or predominantly clear cell RCC, treated for the first time with pazopanib.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Clinical trial eligible population (CTE)

Arm description:

Clinical trial eligible population

Arm type	prospective observational study
Investigational medicinal product name	pazopanibo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients with advanced or metastatic clear cell or predominantly clear cell RCC were enrolled and received at least one dose of pazopanib.

Arm title	Non-clinical trial eligible population (NCTE)

Arm description:

Non-clinical trial eligible population. The NCTE population comprised of patients who did not meet the inclusion/exclusion criteria , or had missing data.

Arm type	prospective observational study
Investigational medicinal product name	pazopanibo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients with advanced or metastatic clear cell or predominantly clear cell RCC were enrolled and received at least one dose of pazopanib.

Number of subjects in period 1	Clinical trial eligible population (CTE)	Non-clinical trial eligible population (NCTE)
Started	97	560
Completed	78	423
Not completed	19	137
Physician decision	1	16
Consent withdrawn by subject	6	49
Other, unspecified	2	20
Lost to follow-up	10	52

Baseline characteristics

Reporting groups	
Reporting group title	Clinical trial eligible population (CTE)
Reporting group description:	
Clinical trial eligible population	
Reporting group title	Non-clinical trial eligible population (NCTE)
Reporting group description:	
Non-clinical trial eligible population. The NCTE population comprised of patients who did not meet the inclusion/exclusion criteria , or had missing data.	

Reporting group values	Clinical trial eligible population (CTE)	Non-clinical trial eligible population (NCTE)	Total
Number of subjects	97	560	657
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	239	281
From 65-84 years	53	307	360
85 years and over	2	14	16
Age continuous Units: years			
arithmetic mean	66.7	65.9	
standard deviation	± 11.10	± 11.03	-
Gender categorical Units: Subjects			
Female	27	181	208
Male	70	379	449

End points

End points reporting groups

Reporting group title	Clinical trial eligible population (CTE)
Reporting group description: Clinical trial eligible population	
Reporting group title	Non-clinical trial eligible population (NCTE)
Reporting group description: Non-clinical trial eligible population. The NCTE population comprised of patients who did not meet the inclusion/exclusion criteria , or had missing data.	
Subject analysis set title	All treated population
Subject analysis set type	Full analysis
Subject analysis set description: Patients treated with at least one dose of pazopanib.	
Subject analysis set title	Measurable disease population
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients who had measurable disease at baseline.	

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)[1]
End point description: PFS is defined as the time (months) to the earliest date of disease progression or death due to any cause from the date of first treatment with pazopanib. The event is the earliest between disease progression and death due to any cause from the first treatment with pazopanib	
End point type	Primary
End point timeframe: Baseline up to 30 months	

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: No statistical analyses have been reported for this primary end point.

End point values	All treated population			
Subject group type	Subject analysis set			
Number of subjects analysed	657			
Units: months				
median (confidence interval 95%)	10.3 (9.2 to 12.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description: Overall survival (OS) is defined the time (months) to death due to any cause from the date of first treatment with pazopanib. The event is death due to any cause from the first treatment with pazopanib.	

End point type	Secondary

End point timeframe:

Baseline up to 30 months

End point values	All treated population			
Subject group type	Subject analysis set			
Number of subjects analysed	657[2]			
Units: months				
median (confidence interval 95%)	29.9 (24.7 to 99.99)			

Notes:

[2] - 99.99 = Not reached (NR)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) among patients with measurable disease at baseline (Measurable disease patients)

End point title	Overall response rate (ORR) among patients with measurable disease at baseline (Measurable disease patients)

End point description:

ORR was defined as the percentage of patients with best overall response.

End point type	Secondary

End point timeframe:

Baseline up to 30 months

End point values	Measurable disease population			
Subject group type	Subject analysis set			
Number of subjects analysed	554			
Units: Percentage of patients				
number (not applicable)	30.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) among patients with measurable disease at baseline

End point title	Duration of response (DOR) among patients with measurable

	disease at baseline

End point description:

Duration of response is the time from the first observed confirmed response to disease progression or death due to any reason.

End point type	Secondary

End point timeframe:

Baseline up to 30 months

End point values	Measurable disease population			
Subject group type	Subject analysis set			
Number of subjects analysed	554			
Units: months				
number (confidence interval 95%)	11 (8.6 to 14.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) among patients with measurable disease at baseline

End point title	Time to response (TTR) among patients with measurable disease at baseline

End point description:

Time to response is defined as the time from enrollment to the date of first documented response.

End point type	Secondary

End point timeframe:

Baseline up to 30 months

End point values	Measurable disease population			
Subject group type	Subject analysis set			
Number of subjects analysed	554			
Units: months				
number (confidence interval 95%)	3 (2.9 to 3.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Daily dose and relative dose intensity (RDI)

End point title	Daily dose and relative dose intensity (RDI)

End point description:

RDI is the ratio of average daily dose of pazopanib during the entire treatment period (including the temporary interruptions) to the recommended daily dose of pazopanib (800 mg).

End point type	Secondary

End point timeframe:

Baseline up to 30 months

End point values	All treated population			
Subject group type	Subject analysis set			
Number of subjects analysed	657			
Units: percentage (%)				
number (not applicable)				
< 85%	41.4			
≥ 85%	58.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in health related quality of life (HRQoL): EQ-5D (3L) and EQ-5D VAS

End point title	Change in health related quality of life (HRQoL): EQ-5D (3L) and EQ-5D VAS

End point description:

Health-related quality of life (HRQoL) was assessed using the EQ-5D (3L) Index and VAS.
The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems.
The EQ-VAS is a vertical visual analogue scale that takes values between 100 (best imaginable health) and 0 (worst imaginable health), on which patients provide a global assessment of their health.
EQ-5D index and VAS scores: the higher the score the better the status. A positive change indicates improvement.

End point type	Secondary

End point timeframe:

Baseline up to 30 months

End point values	All treated population			
Subject group type	Subject analysis set			
Number of subjects analysed	657[3]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
EQ-5D (3L) - 6 months follow-up	-0.03 (± 0.196)			
EQ-5D (3L) - 12 months follow-up	-0.01 (± 0.179)			
EQ-5D (3L) - 24 months follow-up	-0.00 (± 0.144)			
EQ-5D VAS - 6 months follow-up	-1.00 (± 19.926)			
EQ-5D VAS - 12 months follow-up	1.52 (± 21.373)			
EQ-5D VAS - 24 months follow-up	2.86 (± 19.660)			

Notes:

[3] - EQ-5D (3L) n= 364, 261, 153; EQ-5D VAS n= 356, 258, 148

Statistical analyses

No statistical analyses for this end point

Secondary: Change in health related quality of life (HRQoL):FACT-Kidney Symptom Index-19 (FKSI-19) and : FACT-Kidney Symptom Index-Disease-Related Symptoms (FKSI-DRS) score

End point title	Change in health related quality of life (HRQoL):FACT-Kidney Symptom Index-19 (FKSI-19) and : FACT-Kidney Symptom Index-Disease-Related Symptoms (FKSI-DRS) score

End point description:

The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. Participants are asked to respond to 12 questions ("I have a lack of energy," "I feel pain," for example) by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 48). Higher scores represent better health. A negative change from Baseline represents a worsening of condition.
(FKSI-DRS) is a set of items to assess symptoms experienced by patients with advanced kidney cancer. These symptoms include fatigue, pain, weight loss, dyspnea, cough, fever and hematuria. Each item is scored on a 5-point scale (0 = not at all; 4 = very much). The FKSI-DRS total score ranges from 0 (most severe symptoms) to 36 (no symptoms).
Higher scores represent better health. A negative change from Baseline represents a worsening of condition.

End point type	Secondary

End point timeframe:

Baseline up to 30 months

End point values	All treated population			
Subject group type	Subject analysis set			
Number of subjects analysed	657[4]			
Units: scores on a scale				
arithmetic mean (standard deviation)				

FKSI-19 total score - 6 months follow-up	-1.97 (± 10.351)			
FKSI-19 total score - 12 months follow-up	-1.75 (± 9.877)			
FKSI-19 total score - 24 months follow-up	0.07 (± 9.038)			
FKSI-DRS score - 6 months follow-up	-0.45 (± 6.839)			
FKSI-DRS score - 12 months follow-up	-0.35 (± 6.969)			
FKSI-DRS score - 24 months follow-up	0.88 (± 6.681)			

Notes:

[4] - FKSI-19 total score/ FKSI-DRS score n= 355, 258, 150

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of serious adverse events (SAEs) and adverse events of special interest (AESIs) in patients treated with pazopanib

End point title	Frequency of serious adverse events (SAEs) and adverse events of special interest (AESIs) in patients treated with pazopanib

End point description:

SAE is defined as an event that meets 1 of the following criteria: is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions, constitutes a congenital anomaly or birth defect,is a medically important event that may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the outcomes listed above. AESIs were defined as:

- Evidence of liver toxicity (e.g., increased ALT and/or AST, liver failure).
- New onset or worsened hypertension.
- Cardiac dysfunction (e.g., decreased left ventricular function, congestive heart failure).
- Thyroid dysfunction.
- Any other AE that results in a pazopanib dose modification or discontinuation.

End point type	Secondary

End point timeframe:

Baseline up to 30 months; up to 30 days after discontinuation of study drug.

End point values	All treated population			
Subject group type	Subject analysis set			
Number of subjects analysed	657			
Units: percentage of participants				
number (not applicable)				
SAE	9.7			
AESI	54.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 30 months; up to 30 days after discontinuation of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	All Treated Patients

Reporting group description:

All Treated Patients

Serious adverse events	All Treated Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	182 / 657 (27.70%)		
number of deaths (all causes)	284		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to bone			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neoplasm progression				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vascular disorders				
Arteriovenous fistula				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypertension				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Malignant hypertension				

subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Nephrectomy			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleurodesis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toe amputation			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Death			
subjects affected / exposed	4 / 657 (0.61%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		

Disease progression				
subjects affected / exposed	14 / 657 (2.13%)			
occurrences causally related to treatment / all	3 / 15			
deaths causally related to treatment / all	3 / 10			
General physical health deterioration				
subjects affected / exposed	6 / 657 (0.91%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 3			
Impaired healing				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Stenosis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	5 / 657 (0.76%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			

Haemoptysis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiccups			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraneoplastic pleural effusion			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pleural effusion			
subjects affected / exposed	6 / 657 (0.91%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	4 / 657 (0.61%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		
Pulmonary oedema			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	4 / 657 (0.61%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			

Device dislocation			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Liver function test increased			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cervical vertebral fracture			

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Femur fracture				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shunt thrombosis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrioventricular block complete				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				

subjects affected / exposed	6 / 657 (0.91%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Mitral valve incompetence			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	3 / 657 (0.46%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Myocardial ischaemia			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Basal ganglia haemorrhage			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	7 / 657 (1.07%)		
occurrences causally related to treatment / all	2 / 7		
deaths causally related to treatment / all	0 / 1		
Dizziness			

subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic cerebral infarction				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral motor neuropathy				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Posterior reversible encephalopathy syndrome				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				

subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	3 / 657 (0.46%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 657 (0.61%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 657 (0.46%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

Duodenitis haemorrhagic			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocutaneous fistula			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric perforation			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiatus hernia			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Jejunal perforation			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal haemorrhage			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine perforation			

subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Oesophageal fistula				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal ulcer				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				

subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	4 / 657 (0.61%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic foot			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyoderma gangrenosum			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin ulcer			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	5 / 657 (0.76%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 2		
Anuria			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder obstruction			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
End stage renal disease			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nephrotic syndrome			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	3 / 657 (0.46%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			

subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Thyroid disorder			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	4 / 657 (0.61%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint lock			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Osteitis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Necrotising fasciitis				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Peritonsillar abscess				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	7 / 657 (1.07%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 1			
Postoperative wound infection				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psoas abscess				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Sepsis				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Splenic infection				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Dehydration				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				

subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypoglycaemia			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	All Treated Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	286 / 657 (43.53%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	71 / 657 (10.81%)		
occurrences (all)	85		
Aspartate aminotransferase increased			
subjects affected / exposed	45 / 657 (6.85%)		
occurrences (all)	51		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	42 / 657 (6.39%)		
occurrences (all)	50		
Vascular disorders			
Hypertension			

subjects affected / exposed occurrences (all)	148 / 657 (22.53%) 180		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 82 / 657 (12.48%) 114 35 / 657 (5.33%) 39		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 40 / 657 (6.09%) 44		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2014	To clarify inclusion criteria, revised sample size assumptions and enrollment period. Clarification of post progression efficacy data and updated recommended schedule of events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported