



Clinical trial results:

An open-label study to investigate the pharmacodynamics of a repeat dose regimen of bevacizumab (10mg/kg q2w) and escalating repeat doses of pazopanib in renal cell carcinoma

Summary

EudraCT number	2008-005053-38
Trial protocol	GB
Global end of trial date	01 November 2013

Results information

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	17 May 2015

Trial information

Trial identification

Sponsor protocol code	VDF111687
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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	12 February 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the pharmacodynamic effect of bevacizumab (10mg/kg q2w) on various tumor characteristics in subjects with renal cell carcinoma who experience tumour progression on previous first-line (or greater) therapy.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 2009
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	United Kingdom: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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)	9
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study is comprised of Part I and Part II followed by the Maintenance Phase. Participants (Par.) were administered bevacizumab 10 milligrams (mg)/kilogram (kg) during Part I and were randomized to receive pazopanib as escalating repeat doses during Part II and pazopanib in repeating 3-week cycles during the Part II Maintenance Phase.

Period 1

Period 1 title	Part I
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Bevacizumab
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Arm description:

In Part I participants received 3 infusions of 10 mg/kg bevacizumab administered at 2-week intervals.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10mg/Kg every two weeks for a total of 3 infusions

Number of subjects in period 1^[1]	Bevacizumab
Started	9
Completed	9

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 11 participants were enrolled and a total of 9 participants received at least one dose of bevacizumab.

Period 2

Period 2 title	Part II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Pazopanib full cycle
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Arm description:

Following a 14-day washout, participants entering Part II were randomized to receive treatment throughout each 3-week cycle (Group 1). Participants were administered escalating doses of pazopanib, which increased in a stepwise manner in 3-week cycles as follows: 1) 200 mg twice weekly (bid), 2) 200 mg every other day, 3) 200 mg once daily (qd), 4) 400 mg qd, 5) 800 mg qd, and 6) 1200 mg qd. During the Part II Maintenance Phase, 800 mg qd pazopanib was administered in repeating 3-week cycles.

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:

Group1 (3 week cycle)
 200 mg twice weekly for full cycle
 200 mg qod for full cycle
 200 mg qd for full cycle
 400 mg qd for full cycle
 800 mg qd for full cycle
 1200 mg qd for full cycle
 Maintenance phase 800 mg qd for full cycle

Arm title	Pazopanib first 2 weeks
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Arm description:

Following a 14-day washout, participants entering Part II were randomized to receive treatment for the first 2 weeks of each cycle only, i.e., discontinuous dosing (Group 2). Participants were administered escalating doses of pazopanib, which increased in a stepwise manner in 3-week cycles as follows: 1) 200 mg twice weekly (bid), 2) 200 mg every other day, 3) 200 mg once daily (qd), 4) 400 mg qd, 5) 800 mg qd, and 6) 1200 mg qd. During the Part II Maintenance Phase, 800 mg qd pazopanib was administered in repeating 3-week cycles.

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:

Group 2 (dosed 2/3 week cycle)
 200 mg twice weekly for 2 weeks
 200 mg qod for 2 weeks
 200 mg qd for 2 weeks
 400 mg qd for 2 weeks
 800 mg qd for 2 weeks
 1200 mg qd for 2 weeks
 Maintenance phase 800 mg qd for full cycle

Number of subjects in period 2	Pazopanib full cycle	Pazopanib first 2 weeks
Started	4	5
Completed	1	4
Not completed	3	1
Physician decision	2	-
Met Protocol-defined Stopping Criteria	1	-

Lack of efficacy	-	1
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Baseline characteristics

Reporting groups

Reporting group title	Bevacizumab
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Reporting group description:

In Part I participants received 3 infusions of 10 mg/kg bevacizumab administered at 2-week intervals.

Reporting group values	Bevacizumab	Total	
Number of subjects	9	9	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	56.2		
standard deviation	± 8.61	-	
Gender categorical			
Units: Subjects			
Female	4	4	
Male	5	5	
Race			
Units: Subjects			
African American/African Heritage	1	1	
White-White/Caucasian/European Heritage	8	8	

End points

End points reporting groups

Reporting group title	Bevacizumab
Reporting group description: In Part I participants received 3 infusions of 10 mg/kg bevacizumab administered at 2-week intervals.	
Reporting group title	Pazopanib full cycle
Reporting group description: Following a 14-day washout, participants entering Part II were randomized to receive treatment throughout each 3-week cycle (Group 1). Participants were administered escalating doses of pazopanib, which increased in a stepwise manner in 3-week cycles as follows: 1) 200 mg twice weekly (bid), 2) 200 mg every other day, 3) 200 mg once daily (qd), 4) 400 mg qd, 5) 800 mg qd, and 6) 1200 mg qd. During the Part II Maintenance Phase, 800 mg qd pazopanib was administered in repeating 3-week cycles.	
Reporting group title	Pazopanib first 2 weeks
Reporting group description: Following a 14-day washout, participants entering Part II were randomized to receive treatment for the first 2 weeks of each cycle only, i.e., discontinuous dosing (Group 2). Participants were administered escalating doses of pazopanib, which increased in a stepwise manner in 3-week cycles as follows: 1) 200 mg twice weekly (bid), 2) 200 mg every other day, 3) 200 mg once daily (qd), 4) 400 mg qd, 5) 800 mg qd, and 6) 1200 mg qd. During the Part II Maintenance Phase, 800 mg qd pazopanib was administered in repeating 3-week cycles.	

Primary: Percent change from Baseline in tumor size at the Follow-up Visit

End point title	Percent change from Baseline in tumor size at the Follow-up Visit ^[1]
End point description: Computed tomography (CT) is the standard clinical imaging modality for staging and follow-up of participants with renal cell carcinoma (RCC). In part I, CT was used to acquire images of the chest, abdomen, and pelvis after intravenous administration of iodine based contrast medium to monitor changes in tumor size in response to treatment. Tumor size was calculated by summing the longest diameters of all target lesions on the CT scan and expressed as a percent reduction from Baseline.	
End point type	Primary
End point timeframe: Baseline and Follow-up Visit in Part I (assessed up to 6 weeks)	
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 Analysis is not applicable for this Outcome Measure.	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[2]			
Units: % change				
arithmetic mean (confidence interval 95%)	3.65 (-5.12 to 12.42)			

Notes:

[2] - Safety Population: all participants who received at least one dose of bevacizumab.

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in transfer constant from plasma to extracellular space (Ktrans) at 4 hours post-dose and 3 days post-dose in Part I

End point title	Change from Baseline in transfer constant from plasma to extracellular space (Ktrans) at 4 hours post-dose and 3 days post-dose in Part I ^[3]
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End point description:

Change in tumor perfusion was assessed by estimation of Ktrans using Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI). DCE-MRI enables noninvasive assessment of tumor perfusion and microvascular permeability and can help predict response to novel chemotherapy agents. An early increase in tumor perfusion was shown to correlate with tumor response following conventional chemoradiotherapy. In Part I, marker lesions (larger than 2 centimeters [cm]) were chosen to perform quantitative analysis producing estimates of Ktrans as seen on DCE-MRI and was measured at Baseline (2 measurements at Baseline separated by at least 24 hours), at 4 hours post-dose and 3 days post-dose. Mean Baseline (the mean of the two Baseline measurements) was used for summarizing these data.

End point type	Primary
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End point timeframe:

Baseline, 4 hours post-dose and 3 days post-dose in Part I

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 Analysis is not applicable for this Outcome Measure.

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[4]			
Units: 1/minute				
arithmetic mean (confidence interval 95%)				
Mean Baseline	0.157 (0.1025 to 0.2115)			
4 hours post-dose	0.1394 (0.0845 to 0.1944)			
3 days post-dose	0.123 (0.0747 to 0.1713)			

Notes:

[4] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a best response as assessed by the independent reviewer

End point title	Number of participants with a best response as assessed by the independent reviewer
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End point description:

Response was assessed by the independent reviewer according to Evaluation Criteria In Solid Tumors (RECIST), version 1.1. As per RECIST, complete response (CR): disappearance of all target lesions, partial response (PR): at least a 30% decrease in the sum of the longest diameter (LD) of target lesions; progressive disease (PD): at least a 20% increase in the sum of the LD of target lesions; stable disease (SD) implies neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, were assessed.

End point type	Secondary
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End point timeframe:

Day 10 of Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[5]			
Units: Participants				
CR	0			
PR	0			
SD	7			
PD	2			
Not Evaluable	0			
Unknown	0			

Notes:

[5] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of tumor size by vascular volume

End point title	Measurement of tumor size by vascular volume
End point description:	
CT is the standard clinical imaging modality for staging and follow-up of participants with RCC. CT was used to acquire images of the chest, abdomen, and pelvis after intravenous administration of iodine based contrast medium to monitor changes in vascular volume in response to treatment. This was an optional parameter and was not analyzed.	
End point type	Secondary
End point timeframe:	
Baseline and Follow-up Visit in Part I (assessed up to 6 weeks)	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[6]			
Units: cubic millimeter (mm ³)				
arithmetic mean (standard deviation)	()			

Notes:

[6] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of tumor size by tumor volume

End point title	Measurement of tumor size by tumor volume
End point description:	
MRI is widely available in clinical settings and enables evaluation of tumor characteristics, including	

perfusion, microvascular permeability, necrosis, and cellularity. This was an optional parameter and was not analyzed.

End point type	Secondary
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End point timeframe:

Baseline and Follow-up Visit in Part I (assessed up to 6 weeks)

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[7]			
Units: mm ³				
arithmetic mean (standard deviation)	()			

Notes:

[7] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in contrast efflux from tumor (kep)

End point title	Change from Baseline in contrast efflux from tumor (kep)
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End point description:

Changes in tumor perfusion was assessed by estimation of kep using DCE-MRI. DCE-MRI enables noninvasive assessment of tumor perfusion and microvascular permeability and can help predict response to novel chemotherapy agents. An early increase in tumor perfusion was shown to correlate with tumor response following conventional chemo-radiotherapy. Marker lesions (larger than 2 cm) were chosen to perform quantitative analysis producing estimates of kep as seen on DCE-MRI and was measured at Baseline (2 measurements at Baseline separated by at least 24 hours), at 4 hours post dose and 3 days post-dose. Mean Baseline (the mean of the two Baseline measurements) was used for summarizing these data.

End point type	Secondary
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End point timeframe:

Baseline, 4 hours post-dose and 3 days post-dose in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[8]			
Units: 1/Minute				
arithmetic mean (confidence interval 95%)				
Mean Baseline	0.5132 (0.407 to 0.6193)			
4 hour post-dose	0.4671 (0.3626 to 0.5717)			
3 days post-dose	0.4603 (0.2834 to 0.6373)			

Notes:

[8] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in fractional volume of extravascular-extracellular space (Ve)

End point title	Change from Baseline in fractional volume of extravascular-extracellular space (Ve)
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End point description:

Changes in tumor perfusion was assessed by estimation of Ve using Dynamic Contrast-Enhanced MRI (DCE-MRI). DCE-MRI enables noninvasive assessment of tumor perfusion and microvascular permeability and can help predict response to novel chemotherapy agents. An early increase in tumor perfusion was shown to correlate with tumor response following conventional chemo-radiotherapy. Marker lesions (larger than 2 cm) were chosen to perform quantitative analysis producing estimates of Ve as seen on DCE-MRI and was measured at Baseline (2 measurements at Baseline separated by at least 24 hours), at 4 hours post-dose and 3 days post-dose. Mean Baseline (the mean of the two Baseline measurements) was used for summarizing these data.

End point type	Secondary
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End point timeframe:

Baseline, 4 hours post-dose and 3 days post-dose in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[9]			
Units: Unitless				
arithmetic mean (confidence interval 95%)				
Mean Baseline	0.3032 (0.2494 to 0.357)			
4 hours post-dose	0.2772 (0.2198 to 0.3346)			
3 days post- dose	0.281 (0.1836 to 0.3784)			

Notes:

[9] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in initial area under the concentration curve at 90 seconds after injection of contrast agent (IAUC90)

End point title	Change from Baseline in initial area under the concentration curve at 90 seconds after injection of contrast agent (IAUC90)
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End point description:

Changes in tumor perfusion was assessed by estimation of IAUC90 using DCE-MRI. DCE-MRI enables noninvasive assessment of tumor perfusion and microvascular permeability and can help predict response to novel chemotherapy agents. An early increase in tumor perfusion was shown to correlate with tumor response following conventional chemo-radiotherapy. Marker lesions (larger than 2 cm) were chosen to perform quantitative analysis producing estimates of IAUC90 as seen on DCE-MRI and was measured at Baseline (2 measurements at Baseline separated by at least 24 hours), at 4 hours post-dose and 3 days post-dose. Mean Baseline (the mean of the two Baseline measurements) was used for summarizing these data.

End point type	Secondary
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End point timeframe:

Baseline, 4 hours post-dose and 3 days post-dose in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[10]			
Units: Millimoles/liter/second (MMOL/L/S)				
arithmetic mean (confidence interval 95%)				
Mean Baseline	52.69 (36.32 to 69.06)			
4 hours post-dose	47.71 (33.66 to 61.76)			
3 days post-dose	42.58 (27.59 to 57.56)			

Notes:

[10] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in plasma volume (Vp)

End point title	Change from Baseline in plasma volume (Vp)
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End point description:

Changes in tumor perfusion was assessed by estimation of Vp using DCE-MRI. DCE-MRI enables noninvasive assessment of tumor perfusion and microvascular permeability and can help predict response to novel chemotherapy agents. An early increase in tumor perfusion was shown to correlate with tumor response following conventional chemo-radiotherapy. Marker lesions (larger than 2 cm) were chosen to perform quantitative analysis producing estimates of Vp as seen on DCE-MRI and was measured at Baseline (2 measurements at Baseline separated by at least 24 hours), at 4 hours post-dose and 3 days post-dose. Mean Baseline (the mean of the two Baseline measurements) was used for summarizing these data.

End point type	Secondary
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End point timeframe:

Baseline, 4 hours post-dose and 3 days post-dose in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[11]			
Units: Unitless				
arithmetic mean (confidence interval 95%)				
Mean Baseline	0.0309 (0.0155 to 0.0463)			
4 hour post-dose	0.0292 (0.0176 to 0.0409)			
3 days post-dose	0.0227 (0.0098 to 0.0355)			

Notes:

[11] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor perfusion (F) using [15O]Water-positron emission tomography (PET)

End point title	Tumor perfusion (F) using [15O]Water-positron emission tomography (PET)
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End point description:

[15O]Water-PET is used to measure tumor blood flow including detection of changes in blood flow during anti-angiogenic therapy in different tumor settings. A radial arterial line was inserted using sterile technique prior to the [15O]Water-PET. The total volume of blood collected during a scan was approximately 40 milliliters (mL) for [15O]Water-PET. The [15O]Water-PET regional blood flow parameter was only available for one participant at both time points and for a single time point for one other participant and so this data was not analyzed.

End point type	Secondary
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End point timeframe:

Baseline and Day 3 in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[12]			
Units: 1/min				
arithmetic mean (standard deviation)	()			

Notes:

[12] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor Distribution volume (VT) by [15O]Water-positron emission tomography (PET)

End point title	Tumor Distribution volume (VT) by [15O]Water-positron emission tomography (PET)
End point description: [15O]Water-PET is used to measure tumor blood flow including detection of changes in blood flow during anti-angiogenic therapy in different tumor settings. A radial arterial line was inserted using sterile technique prior to the [15O]Water-PET. The total volume of blood collected during a scan was approximately 40 mL for [15O]Water-PET. The [15O]Water-PET regional blood flow parameter was only available for one participant at both time points and for a single time point for one other participant and so this data was not analyzed.	
End point type	Secondary
End point timeframe: Baseline and Day 3 in Part I	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[13]			
Units: 1/min				
arithmetic mean (standard deviation)	()			

Notes:

[13] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Regional blood flow by [15O]Water-positron emission tomography (PET)

End point title	Regional blood flow by [15O]Water-positron emission tomography (PET)
End point description: [15O]Water-PET is used to measure tumor blood flow including detection of changes in blood flow during anti-angiogenic therapy in different tumor settings. A radial arterial line was inserted using sterile technique prior to the [15O]Water-PET. The total volume of blood collected during a scan was approximately 40 mL for [15O]Water-PET. The [15O]Water-PET regional blood flow parameter was only available for one participant at both time points and for a single time point for one other participant and so this data was not analyzed.	
End point type	Secondary
End point timeframe: Baseline and Day 3 in Part I	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[14]			
Units: 1/min				
arithmetic mean (standard deviation)	()			

Notes:

[14] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of glucose metabolic rate by 18F-fluoro-2-deoxy-D-glucose-positron emission tomography ([18F]FDG-PET)

End point title	Measurement of glucose metabolic rate by 18F-fluoro-2-deoxy-D-glucose-positron emission tomography ([18F]FDG-PET)
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End point description:

Glucose metabolism in malignancy differs from that in normal tissue due to alterations in glycolytic enzymes and increased expression of glucose transport proteins, leading to increased glucose uptake and consumption in cancer. PET imaging using [18F]FDG provides a quantitative assessment of tumor metabolism. As glucose metabolic rate within a tumor is not quantified directly, a surrogate measure of glucose metabolism was reported, maximum standardized uptake value (SUV; image value normalised by injected activity and weight or body surface area). Glucose metabolic rate was assessed at Baseline and the Follow-up Visit in Part I.

End point type	Secondary
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End point timeframe:

Baseline and Follow-up Visit in Part I (assessed up to 6 weeks)

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[15]			
Units: Ratio				
arithmetic mean (confidence interval 95%)				
Baseline	13.04 (3.68 to 22.41)			
Part I Follow-up	15.66 (7.22 to 24.09)			

Notes:

[15] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor hypoxia (ratio of tissue to blood [T/ B]) parameters

End point title	Tumor hypoxia (ratio of tissue to blood [T/ B]) parameters
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End point description:

[18F] fluoromisonidazole (FMISO), a nitroimidazole derivative, enables PET imaging of hypoxia in tumors outside the central nervous system. A radial arterial line was inserted using sterile technique prior to [18F]FMISO-PET procedures. The total volume of blood collected during a scan was approximately 75 mL for [18F]FMISO-PET. Tissue clearance (K1), FMISO trapping rate constant, (K3) and net irreversible uptake rate constant (Ki) are respresented here.

End point type	Secondary
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End point timeframe:

Baseline and Day 3 in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[16]			
Units: 1/Minute				
arithmetic mean (confidence interval 95%)				
K1, Baseline	0.2588 (0.1143 to 0.4034)			
K1, Part 1 Day 3	0.1791 (0.0535 to 0.3048)			
K3, Baseline	0.0127 (-0.0112 to 0.0365)			
K3, Part 1 Day 3	0.0101 (-0.0052 to 0.0255)			
Ki, Baseline	0.0037 (-0.0019 to 0.0092)			
Ki, Part 1 Day 3	0.004 (-0.0013 to 0.0093)			

Notes:

[16] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor hypoxia (ratio of tissue to blood (T/ B) parameters- standardized uptake value (SUV) ratio

End point title	Tumor hypoxia (ratio of tissue to blood (T/ B) parameters- standardized uptake value (SUV) ratio
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End point description:

[18F]FMISO, a nitroimidazole derivative, enables PET imaging of hypoxia in tumors outside the central nervous system. A radial arterial line was inserted using sterile technique prior to [18F]FMISO-PET procedures. The total volume of blood collected during a scan was approximately 75 mL for [18F]FMISO-PET. Mean SUV and maximum (Max) SUV is presented here.

End point type	Secondary
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End point timeframe:

Baseline and Day 3 in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[17]			
Units: grams per cubic centimeter (g/cm ³)				
arithmetic mean (confidence interval 95%)				
Mean SUV, Baseline	1.792 (0.3982 to 3.1858)			
Mean SUV, Part 1 Day 3	2.1119 (0.3709 to 3.8529)			
Max SUV, Baseline	2.6334 (0.7518 to 4.5151)			
Max SUV, Part 1 Day 3	3.0703 (0.6965 to 5.4441)			

Notes:

[17] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor hypoxia as measured by apparent diffusion coefficient (ADC) using diffusion weighted imaging (DWI)

End point title	Tumor hypoxia as measured by apparent diffusion coefficient (ADC) using diffusion weighted imaging (DWI)
End point description:	
DWI was acquired prior to contrast agent administration. At least four different b-values were selected within the range 0-1000 second (s)/mm^2. Values for ADC (in mm^2/second) and maps were calculated from the images acquired with the different b-values. Mean Baseline (the mean of the two Baseline measurements) is used for summarizing these data.	
End point type	Secondary
End point timeframe:	
Baseline, 4 hours post-dose and 3 days post-dose in Part I	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[18]			
Units: micrometres squared/second (UM ² /SEC)				
arithmetic mean (confidence interval 95%)				
Mean Baseline, n = 8	1162.59 (1015.98 to 1309.21)			
4 hours post-dose, n = 8	1096.69 (924.81 to 1268.57)			
3 days post-dose, n = 7	1158.14 (965.21 to 1351.08)			

Notes:

[18] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Analysis of plasma and serum biomarkers - IL8, KGF, M65, PDGFbb, P1GF, SDF1b, Tie2, VEGFA, VEGFC, VEGFD, VEGFR1, VEGFR2

End point title	Analysis of plasma and serum biomarkers - IL8, KGF, M65, PDGFbb, P1GF, SDF1b, Tie2, VEGFA, VEGFC, VEGFD, VEGFR1, VEGFR2
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End point description:

The blood borne biomarkers were reviewed graphically but not summarized.

End point type	Secondary
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End point timeframe:

From the time of the first infusion of bevacizumab until Day 1 of Cycle 8 in Part II (up to 24 weeks)

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[19]			
Units: pg/mL (picogram/milliliter)				
arithmetic mean (standard deviation)	()			

Notes:

[19] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating tumor cell levels

End point title	Circulating tumor cell levels
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End point description:

Blood samples (approximately 20 mL) were collected for measurement of circulating tumor cells (CTCs) in whole blood. Measurement of CTCs was to be performed using a validated assay. CTC could not be isolated and therefore whole blood levels of CTC have not been presented.

End point type	Secondary
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End point timeframe:

From the time of the first infusion of bevacizumab until Day 1 of Cycle 8 in Part II (up to 24 weeks)

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[20]			
Units: cells/7.5 millilitres of blood				
arithmetic mean (standard deviation)	()			

Notes:

[20] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor histology results for analyte: Ki67

End point title	Tumor histology results for analyte: Ki67
End point description: CT or ultrasound-guided core needle biopsies were performed to obtain tissue specimens for immunohistological staining for markers of endothelial cells and VEGF signaling. Difference of post-dose and pre-dose are presented.	
End point type	Secondary
End point timeframe: Baseline and Day 10 in Part I	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[21]			
Units: Proportion of cells				
number (not applicable)				
Analyte positive (AP) endothelial cells (EC)	-0.0143			
AP tumor cells	-0.0301			
Proportion (Pro.) of total cells (TC) that are AP	-0.0285			
Pro. of TC tumor cells in images for each analyte	-0.0502			
Pro. of TC that are EC in images for each analyte	-0.0299			

Notes:

[21] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor histology results for analyte: pAKT

End point title	Tumor histology results for analyte: pAKT
End point description: CT or ultrasound-guided core needle biopsies were performed to obtain tissue specimens for immunohistological staining for markers of endothelial cells and VEGF signaling. Difference of post-dose and pre-dose are presented.	
End point type	Secondary

End point timeframe:
Baseline and Day 10 in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[22]			
Units: Proportion of cells				
number (not applicable)				
Analyte positive (AP) endothelial cells (EC)	-0.1841			
AP tumor cells	-0.0756			
Pro. of TC that are AP	-0.0773			
Pro. of TC tumor cells in images for each analyte	0.0099			
Pro. of TC that are EC in images for each analyte	-0.0335			

Notes:

[22] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor histology results for analyte: pERK

End point title	Tumor histology results for analyte: pERK
End point description: CT or ultrasound-guided core needle biopsies were performed to obtain tissue specimens for immunohistological staining for markers of endothelial cells and VEGF signaling. Difference of post-dose and pre-dose are presented.	
End point type	Secondary
End point timeframe: Baseline and Day 10 in Part I	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[23]			
Units: Proportion of cells				
number (not applicable)				
Analyte positive (AP) endothelial cells (EC)	-0.1672			
AP tumor cells	-0.2272			
Pro. of TC that are AP	-0.2103			
Pro. of TC tumor cells in images for each analyte	-0.0201			
Pro. of TC that are EC in images for each analyte	-0.0567			

Notes:

[23] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor histology results for analyte: pSTAT3

End point title	Tumor histology results for analyte: pSTAT3
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End point description:

CT or ultrasound-guided core needle biopsies were performed to obtain tissue specimens for immunohistological staining for markers of endothelial cells and VEGF signaling. Difference of post-dose and pre-dose are presented.

End point type	Secondary
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End point timeframe:

Baseline and Day 10 in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	8 ^[24]			
Units: Proportion of cells				
number (not applicable)				
Analyte positive (AP) endothelial cells (EC)	-0.0035			
AP tumor cells	-0.0739			
Pro. of TC that are AP	-0.0474			
Pro. of TC tumor cells in images for each analyte	0.0049			
Pro. of TC that are EC in images for each analyte	-0.0294			

Notes:

[24] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Bevacizumab pharmacokinetic parameter, elimination rate constant (K)

End point title	Bevacizumab pharmacokinetic parameter, elimination rate constant (K)
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End point description:

Blood samples (approximately 2 mL) for the analysis of bevacizumab was collected in serum collection tubes (no anticoagulant) prior to the infusion (only on study Day 1), between 20 to 70 minutes after the start of the infusion and end of the infusion (or immediately prior to the end of the infusion in the case of pharmacokinetic [PK] samples) on Day 3, Day 15 and Day 29. Bevacizumab plasma concentration-time data were described by a 1-compartment model with first order elimination. Pharmacokinetic (PK) Population: all participants in the Safety Population for whom at least one pharmacokinetic sample was obtained and analyzed.

End point type	Secondary
End point timeframe:	
Day 1, Day 3, Day 15 and Day 29 in Part I	

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[25]			
Units: per day				
number (confidence interval 95%)	0.0477 (0.0406 to 0.0561)			

Notes:

[25] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Bevacizumab pharmacokinetic parameter, volume of systemic compartment (V1)

End point title	Bevacizumab pharmacokinetic parameter, volume of systemic compartment (V1)
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End point description:

Blood samples (approximately 2 mL) for the analysis of bevacizumab was collected in serum collection tubes (no anticoagulant) prior to the infusion (only on study Day 1), between 20 to 70 minutes after the start of the infusion and end of the infusion (or immediately prior to the end of the infusion in the case of PK samples) on Day 15 and Day 29. Bevacizumab plasma concentration-time data were described by a 1-compartment model with first order elimination.

End point type	Secondary
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End point timeframe:

Day 1, Day 3, Day 15 and Day 29 in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[26]			
Units: mL/kg				
number (confidence interval 95%)	72.9 (65.9 to 80.7)			

Notes:

[26] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Bevacizumab plasma parameter, residual variability (RESIDUAL)

End point title	Bevacizumab plasma parameter, residual variability
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End point description:

Blood samples (approximately 2 mL) for the analysis of bevacizumab was collected in serum collection tubes (no anticoagulant) prior to the infusion (only on study Day 1), between 20 to 70 minutes after the start of the infusion and end of the infusion (or immediately prior to the end of the infusion in the case of PK samples) on Day 15 and Day 29. Bevacizumab plasma concentration-time data were described by a 1-compartment model with first order elimination.

End point type Secondary

End point timeframe:

Day 1, Day 3, Day 15 and Day 29 in Part I

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	9 ^[27]			
Units: Unitless				
number (confidence interval 95%)	0.356 (0.293 to 0.419)			

Notes:

[27] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean pre-dose plasma pazopanib concentrations from dose escalation phase of Part II

End point title Mean pre-dose plasma pazopanib concentrations from dose escalation phase of Part II

End point description:

For pharmacokinetic analysis of pazopanib blood samples (approximately 2 mL) were collected in an ethylenediaminetetraacetic acid (EDTA) tube pre-dose on each dosing day and 3 hours post-dose on Day 1 and Day 8.

End point type Secondary

End point timeframe:

Cycle 3 Day 15, Cycle 4 Day 15, Cycle 5 Day 15, Cycle 6 Day 15 in Part II

End point values	Pazopanib full cycle	Pazopanib first 2 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 ^[28]	5 ^[29]		
Units: Nanogram (ng)/mL				
arithmetic mean (standard deviation)				
Cycle 2 Day 15, n= 4, 5	8560.8 (± 7483.5)	4246.2 (± 5145.72)		
Cycle 3 Day 15, n= 4, 5	19197.3 (± 8193.33)	8946.8 (± 6326.35)		
Cycle 4 Day 15, n= 3, 4	20688.3 (± 3331.48)	12596.6 (± 8776.79)		

Cycle 5 Day 15, n= 4, 4	30948.3 (± 8678.94)	19425.3 (± 16845.11)		
Cycle 6 Day 15, n= 4, 4	32823.8 (± 13728.39)	24164.8 (± 19463.53)		

Notes:

[28] - Safety Population

[29] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse event (AE) or serious adverse event (SAE)

End point title	Number of participants with any adverse event (AE) or serious adverse event (SAE)
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End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect or all grade 4 laboratory abnormalities.

End point type	Secondary
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End point timeframe:

From the time of the first infusion of bevacizumab until the last dose of pazopanib treatment (up to Week 111)

End point values	Bevacizumab	Pazopanib full cycle	Pazopanib first 2 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[30]	4 ^[31]	5 ^[32]	
Units: Participants				
Any AE	9	4	5	
Any SAE	0	2	1	

Notes:

[30] - Safety Population

[31] - Safety Population

[32] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with worst-case on-therapy change from Baseline in laboratory parameters

End point title	Number of participants with worst-case on-therapy change from Baseline in laboratory parameters
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End point description:

Laboratory parameters were assessed at Baseline (Day -21 to Day -1 in Part I); Day 1, 15, 29 for Part I and Day 1 of each cycle for Part II. Worst-case on-therapy changes from Baseline in laboratory parameters with respect to the normal ranges are presented. For the indicated test, 99999 (NA) represents that the data was not available.

End point type	Secondary
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End point timeframe:

Baseline until Day 29 for Part I or Day 1 of the last cycle for Part II (up to Week 111)

End point values	Bevacizumab	Pazopanib full cycle	Pazopanib first 2 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[33]	4 ^[34]	5 ^[35]	
Units: Participants				
Chloride-Decrease to Low (DtL)	1	3	1	
Chloride-Increase to High (ItH)	0	0	1	
Lactate Dehydrogenase-DtL	0	0	0	
Lactate Dehydrogenase-ItH	0	3	2	
Total Protein-DtL	0	1	0	
Total Protein-ItH	1	1	0	
Urea/BUN-DtL	0	0	0	
Urea/BUN-ItH	2	0	1	
Uric acid-DtL	0	1	1	
Uric acid-ItH	0	0	1	
Activated Partial Thromboplastin Time-DtL	0	99999	99999	
Activated Partial Thromboplastin Time (ItH)	0	99999	99999	
Free T3-DtL	0	0	0	
Free T3-ItH	0	0	1	
Thyroid Stimulating Hormone-DtL	0	0	0	
Thyroid Stimulating Hormone-ItH	0	1	1	
Basophils-DtL	0	0	0	
Basophils-ItH	0	0	0	
Eosinophils-DtL	0	0	0	
Eosinophils-ItH	0	0	0	
Hematocrit-DtL	0	0	3	
Hematocrit-ItH	0	0	0	
Mean Corpuscle Hemoglobin-DtL	0	0	2	
Mean Corpuscle Hemoglobin-ItH	0	1	2	
Mean Corpuscle Volume-DtL	1	0	0	
Mean Corpuscle Volume-ItH	0	0	1	
Monocytes-DtL	0	0	0	
Monocytes-ItH	1	2	0	
Red Blood Cell count-DtL	0	3	2	
Red Blood Cell count-ItH	1	0	0	
Urine Total Protein/Creatinine ratio-DtL	0	0	0	
Urine Total Protein/Creatinine ratio-ItH	1	2	4	

Notes:

[33] - Safety Population

[34] - Safety Population

[35] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with worst-case on-therapy from Baseline in vital sign parameters

End point title	Number of participants with worst-case on-therapy from Baseline in vital sign parameters
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End point description:

Vital signs included systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate and temperature. Vital sign measurements were taken at Baseline (Day -30 to Day -1 in Part I); Day 1, 8, 15, 29 for Part I and Day 1 of each cycle for Part II. Worst-case on-therapy from Baseline in vital signs are presented here. Worst case on therapy not analysed for temperature; therefore, , the value of 99999 was entered which represents NA.

End point type	Secondary
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End point timeframe:

Baseline until Day 29 for Part I or Day 1 of the last cycle for Part II (up to Week 111)

End point values	Bevacizumab	Pazopanib full cycle	Pazopanib first 2 weeks	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9 ^[36]	4 ^[37]	5 ^[38]	
Units: Participants				
SBP-Any Grade Increase	3	3	4	
SBP- Increase to Grade 3 (≥ 160)	0	0	1	
DBP-Any Grade Increase	4	3	3	
DBP-Increase to Grade 3 (≥ 100)	0	2	1	
Heart rate- Decrease to <60	0	2	1	
Heart rate-Change to Normal or No Change	7	2	3	
Heart rate- Increase to >100	2	1	1	
Temperature	99999	99999	99999	

Notes:

[36] - Safety Population

[37] - Safety Population

[38] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate as an electrocardiogram (ECG) parameter in Part II

End point title	Change from Baseline in heart rate as an electrocardiogram (ECG) parameter in Part II
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End point description:

A single 12-lead ECG was obtained using an ECG machine that automatically calculates the heart rate. Prior to each ECG test, the participant was at rest for approximately 10 minutes. The participant was in the semi-recumbent or supine position; the same position was required for all subsequent ECG tests. 12-Lead ECG was performed only at Baseline (-30 to -1) in Part-I and on Day 1 of Cycle 1 and Day 1 of Cycle 7 in Part-II. Note only 0 or 1 participant was analyzed for the indicated treatment group/time point; therefore, the value of 99999 was entered which represents NA.

End point type	Secondary
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End point timeframe:

Baseline (Cycle 1 Day 1), Cycle 7 Day 1 in Part II

End point values	Pazopanib full cycle	Pazopanib first 2 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 ^[39]	5 ^[40]		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Part 2 Cycle 1 Day 1, n= 3,5	7 (± 9.54)	0.4 (± 6.43)		
Part 2 Cycle 7-50 Day 1, n= 3,4	-5 (± 6.24)	-3.5 (± 5.92)		
Follow-up, n= 0,1	99999 (± 99999)	1 (± 99999)		

Notes:

[39] - Safety Population

[40] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in electrocardiogram parameters (PR, RS, QT, QTcF)

End point title	Change from Baseline in electrocardiogram parameters (PR, RS, QT, QTcF)
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End point description:

A single 12-lead ECG was obtained using an ECG machine that automatically calculates PR Interval (PR), QRS duration (QRS), QT Interval (QT), and corrected QT interval by Fridericia (QTcF) intervals at only Baseline (-30 to -1) in Part I and on Day 1 of Cycle 1 and Day 1 of Cycle 7 in Part-II. Prior to each ECG test, the participant was at rest for approximately 10 minutes. The participant was in the semi-recumbent or supine position; the same position was required for all subsequent ECG tests. Note only 0 or 1 participant was analyzed for the indicated treatment group/time point; therefore, the value of 99999 was entered which represents NA.

End point type	Secondary
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End point timeframe:

Baseline (Cycle 1 Day 1), Cycle 7 Day 1 in Part II

End point values	Pazopanib full cycle	Pazopanib first 2 weeks		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 ^[41]	5 ^[42]		
Units: Milliseconds (msec)				
arithmetic mean (standard deviation)				
PR-Part 2 C1 Day 1, n= 3,5	1.3 (± 12.22)	8.8 (± 16.35)		
PR-Part 2 C7-50 Day 1, n= 3,4	4 (± 14.42)	0.3 (± 9.39)		
PR-Follow-up, n= 0,1	99999 (± 99999)	8 (± 99999)		
QRS-Part 2 C1 Day 1, n= 3,5	0.7 (± 1.15)	3.6 (± 10.33)		
QRS-Part 2 C7-50 Day 1, n= 3,4	0 (± 5.29)	3.5 (± 12.48)		
QRS-Follow-up, n= 0,1	99999 (± 99999)	1 (± 99999)		

QT-Part 2 C1 Day 1, n= 3,5	-13.3 (± 16.65)	-1.6 (± 25.39)		
QT-Part 2 C7-50 Day 1, n= 3,4	21 (± 14.93)	2.8 (± 25.21)		
QT-Follow-up, n= 0,1	99999 (± 99999)	0 (± 99999)		
QTCF-Part 2 C1 Day 1, n= 3,5	-0.7 (± 15.63)	-4.2 (± 12.05)		
QTCF-Part 2 C7-50 Day 1, n= 3,4	-1.7 (± 3.51)	0 (± 11.63)		
QTCF-Follow-up, n= 0,1	99999 (± 99999)	3.3 (± 99999)		

Notes:

[41] - Safety Population

[42] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment AEs

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Bevacizumab
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Reporting group description:

In Part I participants received 3 infusions of 10 mg/kg bevacizumab administered at 2-week intervals.

Reporting group title	Pazopanib full cycle
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Reporting group description:

Following a 14-day washout, participants entering part II were randomized to receive treatment throughout each 3-week cycle (Group 1). Participants were administered escalating doses of pazopanib, which increased in a stepwise manner in 3-week cycles as follows: 1) 200 mg twice weekly (bid), 2) 200 mg every other day, 3) 200 mg once daily (qd), 4) 400 mg qd, 5) 800 mg qd, and 6) 1200 mg qd. During the Part II Maintenance Phase, 800 mg qd pazopanib was administered in repeating 3-week cycles.

Reporting group title	Pazopanib first 2 weeks
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Reporting group description:

Following a 14-day washout, participants entering part II were randomized to receive treatment for the first 2 weeks of each cycle only, i.e., discontinuous dosing (Group 2). Participants were administered escalating doses of pazopanib, which increased in a stepwise manner in 3-week cycles as follows: 1) 200 mg twice weekly (bid), 2) 200 mg every other day, 3) 200 mg once daily (qd), 4) 400 mg qd, 5) 800 mg qd, and 6) 1200 mg qd. During the Part II Maintenance Phase, 800 mg qd pazopanib was administered in repeating 3-week cycles.

Serious adverse events	Bevacizumab	Pazopanib full cycle	Pazopanib first 2 weeks
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	2 / 4 (50.00%)	1 / 5 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Bevacizumab	Pazopanib full cycle	Pazopanib first 2 weeks
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	4 / 4 (100.00%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 9 (11.11%)	2 / 4 (50.00%)	3 / 5 (60.00%)
occurrences (all)	1	2	3
Hypotension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 9 (44.44%)	3 / 4 (75.00%)	3 / 5 (60.00%)
occurrences (all)	4	7	4
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Influenza like illness			
subjects affected / exposed	2 / 9 (22.22%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Oedema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	2 / 4 (50.00%)	1 / 5 (20.00%)
occurrences (all)	1	4	1
Cough			
subjects affected / exposed	2 / 9 (22.22%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	2
Dysphonia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Epistaxis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pneumothorax			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Pulmonary hypertension subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Wheezing subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Investigations Amylase increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 2
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Lipase increased subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 4 (25.00%) 2	0 / 5 (0.00%) 0
Arthropod bite subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Contusion subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0
Excoriation			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Sunburn subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Tricuspid valve incompetence subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 4 (25.00%) 1	2 / 5 (40.00%) 2
Paraesthesia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 4 (25.00%) 1	1 / 5 (20.00%) 1
Burning sensation subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1
Lethargy subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Sciatica subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Anaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Pernicious anaemia			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Eyelid pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Visual impairment			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)	2 / 4 (50.00%)	2 / 5 (40.00%)
occurrences (all)	1	7	5
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)	2 / 4 (50.00%)	4 / 5 (80.00%)
occurrences (all)	1	3	4
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	2 / 4 (50.00%)	2 / 5 (40.00%)
occurrences (all)	0	3	3
Stomatitis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 4 (50.00%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	2
Gingival bleeding			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Toothache			

subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Abdominal pain lower			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Abdominal tenderness			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Paraesthesia oral			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 9 (0.00%)	2 / 4 (50.00%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Dry skin			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Hair colour changes			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Blister			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Miliaria			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Seborrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Skin hypertrophy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Musculoskeletal pain			
subjects affected / exposed	2 / 9 (22.22%)	3 / 4 (75.00%)	0 / 5 (0.00%)
occurrences (all)	2	3	0
Pain in extremity			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	1 / 5 (20.00%)
occurrences (all)	2	1	1
Back pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 4 (50.00%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Osteonecrosis			

subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Spinal pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Flank pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Groin pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Joint swelling			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pain in jaw			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Sinusitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	3
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Oral herpes			
subjects affected / exposed	0 / 9 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	1 / 9 (11.11%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 9 (11.11%)	2 / 4 (50.00%)	2 / 5 (40.00%)
occurrences (all)	1	3	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2009	Removal of pharmacogenetics at request of LREC due to small number of subjects to be recruited and correlations would be limited
27 July 2009	Extension of time line from 7 days to 21 days duration for baseline assessments to reduce the burden on the subjects, addition of previously collected pathology tissue to supplement the pre-treatment information, update to biomarkers to take into account advances in the state of knowledge
14 April 2010	Addition of head CT scan to screening to confirm eligibility, introduction of flexibility to allow inclusion of local safety practices following protocol defined procedures on case by case basis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported