Clinical trial results:
Randomized, Double-Blind Phase 2 Study of Axitinib (AG 013736) With or Without Dose Titration in Patients with Metastatic Renal Cell Carcinoma

Summary

EudraCT number	2008-007786-23
Trial protocol	ES CZ DE
Global end of trial date	29 February 2016

Results information

Result version number	v1 (current)
This version publication date	16 March 2017
First version publication date	16 March 2017

Trial information

Trial identification

Sponsor protocol code	A4061046

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00835978
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 Est 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com

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 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to prospectively evaluate the safety and efficacy of axitinib with and without dose titration in patients with metastatic renal cell carcinoma (mRCC)

Protection of trial subjects:

The study was conducted in accordance with legal and regulatory requirements, as well as the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki as amended by the 52nd World Medical Association (WMA) General Assembly in October 20001.
Informed consent was obtained from each patient (or patient's legally authorized representative) before the patient was admitted to the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 September 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 18
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Japan: 44
Country: Number of subjects enrolled	Russian Federation: 45
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United States: 90
Worldwide total number of subjects	213
EEA total number of subjects	34

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)	136
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 49 centers in Czech Republic, Germany, Japan, Russian Federation, Spain, and United States (US).

Pre-assignment

Screening details:

Participants were enrolled in a 4-week lead-in period, during which they received axitinib 5 milligram (mg) twice a day (BID). After the lead-in period, participants meeting randomization criteria were then randomized to one of the two treatment arms. Participants, not meeting criteria, continued study without dose titration (non-randomized arm).

Period 1

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

Blinding implementation details:

The dose titration in the randomized arms (Arm A and B) was double-blinded. The interactive voice response system (IVRS) assigned study treatment on Cycle 2 Day 1. The IVRS maintained the blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Titration Arm

Arm description:

Participants initially received axitinib 5 mg twice a day (BID) + axitinib (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + axitinib (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + axitinib [blinded therapy] 5 mg BID).

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	AG-013736
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Axitinib 5 mg twice a day (BID) + axitinib (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + axitinib (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + axitinib [blinded therapy] 5 mg BID).

Arm title	Placebo Titration Arm

Arm description:

Participants initially received axitinib 5mg BID + placebo (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + placebo (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + placebo [blinded therapy] 5 mg BID).

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Axitinib 5mg BID + placebo (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + placebo (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + placebo [blinded therapy] 5 mg BID).

Arm title	Non-randomized Arm

Arm description:

Participants not eligible for randomization were assigned to receive axitinib 5 mg BID or a reduced dose per the dose modification guideline. Dose titration was not permitted in this treatment arm.

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	AG-013736
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants not eligible for randomization received axitinib 5 mg BID or a reduced dose per the dose modification guideline. Dose titration was not permitted in this treatment arm.

Arm title	Discontinued Prior to Randomization

Arm description:

Participants who discontinued before they were randomized to any of the treatment or non-randomized arms.

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	AG-013736
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who discontinued before they were randomized to any of the treatment or non-randomized arms.

Number of subjects in period 1	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm
Started	56	56	91
Treated	56	56	91
Completed	0	0	0
Not completed	56	56	91
Consent withdrawn by subject	-	3	-
Adverse event, non-fatal	1	-	1
Death	33	40	49
Not Specified	5	1	8

Study terminated by sponsor	12	8	30
Lost to follow-up	3	4	2
Objective progression or relapse	2	-	1

Number of subjects in period 1	Discontinued Prior to Randomization
Started	10
Treated	10
Completed	0
Not completed	10
Consent withdrawn by subject	5
Adverse event, non-fatal	-
Death	4
Not Specified	-
Study terminated by sponsor	-
Lost to follow-up	1
Objective progression or relapse	-

Baseline characteristics

Reporting groups	
Reporting group title	Active Titration Arm
Reporting group description:	
Participants initially received axitinib 5 mg twice a day (BID) + axitinib (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + axitinib (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + axitinib [blinded therapy] 5 mg BID).	
Reporting group title	Placebo Titration Arm
Reporting group description:	
Participants initially received axitinib 5mg BID + placebo (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + placebo (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + placebo [blinded therapy] 5 mg BID).	
Reporting group title	Non-randomized Arm
Reporting group description:	
Participants not eligible for randomization were assigned to receive axitinib 5 mg BID or a reduced dose per the dose modification guideline. Dose titration was not permitted in this treatment arm.	
Reporting group title	Discontinued Prior to Randomization
Reporting group description:	
Participants who discontinued before they were randomized to any of the treatment or non-randomized arms.	

Reporting group values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm
Number of subjects	56	56	91
Age Categorical Units: Subjects			
< 65 Years	38	38	54
>= 65 Years	18	18	37
Age Continuous Units: Years			
arithmetic mean	59.7	59.6	62.9
standard deviation	± 10.2	± 10.5	± 8.9
Gender, Male/Female Units: Subjects			
Female	19	11	36
Male	37	45	55

Reporting group values	Discontinued Prior to Randomization	Total	
Number of subjects	10	213	
Age Categorical Units: Subjects			
< 65 Years	6	136	
>= 65 Years	4	77	

Age Continuous Units: Years arithmetic mean standard deviation	 62.9 ± 7.5	 -	
Gender, Male/Female Units: Subjects			
Female Male	4 6	70 143	

Subject analysis sets

Subject analysis set title	All Participants
Subject analysis set type	Per protocol

Subject analysis set description:

All enrolled participants (randomized and non-randomized) who received at least one dose of study medication.

Reporting group values	All Participants		
Number of subjects	213		
Age Categorical Units: Subjects			
< 65 Years >= 65 Years			
Age Continuous Units: Years arithmetic mean standard deviation	 61.2 ± 9.7		
Gender, Male/Female Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Active Titration Arm

Reporting group description:

Participants initially received axitinib 5 mg twice a day (BID) + axitinib (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + axitinib (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + axitinib [blinded therapy] 5 mg BID).

Reporting group title	Placebo Titration Arm

Reporting group description:

Participants initially received axitinib 5mg BID + placebo (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + placebo (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + placebo [blinded therapy] 5 mg BID).

Reporting group title	Non-randomized Arm

Reporting group description:

Participants not eligible for randomization were assigned to receive axitinib 5 mg BID or a reduced dose per the dose modification guideline. Dose titration was not permitted in this treatment arm.

Reporting group title	Discontinued Prior to Randomization

Reporting group description:

Participants who discontinued before they were randomized to any of the treatment or non-randomized arms.

Subject analysis set title	All Participants
Subject analysis set type	Per protocol

Subject analysis set description:

All enrolled participants (randomized and non-randomized) who received at least one dose of study medication.

Primary: Objective Response Rate (ORR) - Percentage of Participants With Objective Response

End point title	Objective Response Rate (ORR) - Percentage of Participants With Objective Response[1]

End point description:

ORR was defined as the proportion of participants with objective response based assessment of complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.0). CR was defined as complete disappearance of all target lesions and non-target disease. No new lesions. PR was defined as >=30% decrease on study under baseline of the sum of longest diameters of all target lesions. No unequivocal progression of non-target disease. No new lesions.

End point type	Primary

End point timeframe:

Baseline up to disease progression, death, or withdrawal; performed at baseline and repeated every 8 weeks for 24 weeks, then every 12 weeks.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	All Participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	56	56	91	213
Units: Percentage of Participants				
number (confidence interval 95%)	53.6 (39.7 to 67)	33.9 (21.8 to 47.8)	59.3 (48.5 to 69.5)	48.4 (41.5 to 55.3)

Statistical analyses

Statistical analysis title	Objective Response Rate (ORR)

Statistical analysis description:

ORR for the 2 treatment arms was compared with the Cochran-Mantel-Haenszel test stratified by ECOG performance status. The relative risk ratio estimator was used to contrast the treatment effects on the endpoint. Both a point estimate and a 2-sided 95% CI were calculated using a normal approximation.

Comparison groups	Active Titration Arm v Placebo Titration Arm
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0189 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.578
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.017
upper limit	2.448

Notes:

[2] - A priori defined threshold for statistical significance was: alpha=0.10 (one-sided)

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)[3]

End point description:

The time from first dose administration to first documentation of objective tumor progression or to death due to any cause. PFS in each arm was assessed using the Kaplan-Meier method and estimates of the PFS curves from the Kaplan-Meier method were presented.

End point type	Secondary

End point timeframe:

Baseline up to disease progression, death, or withdrawal; performed at baseline and repeated every 8 weeks for 24 weeks, then every 12 weeks

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	All Participants
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	56	56	91	213
Units: Months				
median (confidence interval 95%)	14.5 (9.2 to 24.5)	15.7 (8.3 to 19.4)	16.6 (11.2 to 22.5)	14.6 (11.5 to 17.5)

Statistical analyses

Statistical analysis title	Progression-Free Survival (PFS)
Comparison groups	Active Titration Arm v Placebo Titration Arm
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2444
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.849
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.535
upper limit	1.348

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)[4]

End point description:

DR was defined as the time from the first documentation of objective tumor response (complete response - CR or Partial response - PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. The median values were estimated based on Kaplan-Meier method. 95% confidence interval was based on the Brookmeyer and Crowley method.

End point type	Secondary

End point timeframe:

Baseline up to disease progression, death, or withdrawal; performed at baseline and repeated every 8 weeks for 24 weeks, then every 12 weeks

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	19	54	
Units: Months				
median (confidence interval 95%)	9999 (10.8 to	21.2 (11.1 to	23.3 (15.7 to	

9999)	25.8)	28.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)[5]

End point description:

OS was defined as the time from date of the first dose of the study medication to date of death due to any cause. For participants who did not die, their survival times were to be censored at the last date they were known to be alive.

End point type	Secondary

End point timeframe:

Baseline up to disease progression, death, or withdrawal; performed at baseline and repeated every 8 weeks for 24 weeks, then every 12 weeks.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	56	91	
Units: Months				
median (confidence interval 95%)	42.7 (24.7 to 9999)	30.4 (23.7 to 45)	41.6 (33 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Axitinib

End point title	Maximum Observed Plasma Concentration (Cmax) of Axitinib[6]

End point description:

Cmax for steady-state axitinib was evaluated on Cycle 2 Day 15. Results were normalized to axitinib 7 mg dose for active titration arm and axitinib 5 mg dose for placebo titration arm. Results were normalized to axitinib 7 mg dose for active titration arm and axitinib 5 mg dose for placebo titration arm.

End point type	Secondary

End point timeframe:

Cycle 2 Day 15 (C2D15): pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: ng/mL				
geometric mean (confidence interval 95%)	31.74 (21.63 to 46.58)	23.05 (16.36 to 32.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax) for Axitinib,

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax) for Axitinib,[7]

End point description:

Tmax for steady-state axitinib was evaluated on Cycle 2 Day 15.

End point type	Secondary

End point timeframe:

C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: hrs				
median (full range (min-max))	2.04 (1 to 6)	2 (0 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUClast) for Axitinib

End point title	Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUClast) for Axitinib[8]

End point description:

Area under the plasma concentration time-curve from zero to the last measurable concentration (AUClast). AUClast for steady-state axitinib was evaluated on Cycle 2 Day 15. Results were normalized

to axitinib 7 mg dose for active titration arm and axitinib 5 mg dose for placebo titration arm.

End point type	Secondary

End point timeframe:

C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: ng.hr/mL				
geometric mean (confidence interval 95%)	105.33 (70.16 to 158.14)	78.44 (54.53 to 112.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to 24 hours[AUC(0-24)] for Axitinib

End point title	Area Under the Curve From Time Zero to 24 hours[AUC(0-24)] for Axitinib[9]

End point description:

Area under the plasma concentration time-curve from zero 24 hours[AUC(0-24). AUC(0-24) for steady-state axitinib was evaluated on Cycle 2 Day 15. Results were normalized to axitinib 7 mg dose for active titration arm and axitinib 5 mg dose for placebo titration arm.

End point type	Secondary

End point timeframe:

C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	14		
Units: ng.hr/mL				
geometric mean (confidence interval 95%)	258.68 (150.47 to 444.72)	161.38 (102.09 to 255.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Decay Half-Life (t1/2) for Axitinib

End point title	Plasma Decay Half-Life (t1/2) for Axitinib[10]

End point description:

Plasma decay half-life is the time measured for the plasma concentration to decrease by one half. Plasma decay half life for steady-state axitinib was evaluated on Cycle 2 Day 15.

End point type	Secondary

End point timeframe:

C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	14		
Units: Hour				
arithmetic mean (standard deviation)	2.48 (± 1.902)	2.81 (± 1.685)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent oral clearance (CL/F) of Axitinib

End point title	Apparent oral clearance (CL/F) of Axitinib[11]

End point description:

Clearance (CL) of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) is influenced by the fraction of the dose absorbed (F). Clearance is defined as the volume of blood from which drug can be completely removed per unit of time. CL/F for steady-state axitinib was evaluated on Cycle 2 Day 15.

End point type	Secondary

End point timeframe:

C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	14		
Units: L/hr				
geometric mean (confidence interval 95%)	54.15 (31.49 to 93.12)	61.93 (39.17 to 97.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of distribution during the elimination phase (Vz/F) for Axitinib

End point title	Apparent volume of distribution during the elimination phase (Vz/F) for Axitinib[12]

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. Vz/F is influenced by the fraction absorbed. Vz/F for steady-state axitinb was evaluated on Cycle 2 Day 15.

End point type	Secondary

End point timeframe:

C2D15: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	14		
Units: Litre				
geometric mean (confidence interval 95%)	158.18 (98.38 to 254.34)	216.62 (145 to 323.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in systolic blood pressure

End point title	Change from baseline in systolic blood pressure[13]

End point description:

Value at respective visit minus value at baseline

End point type	Secondary

End point timeframe:

At screening (D-14 to D-1); lead-in period: Cycle 1 - Day 1 and Day 15; Cycle 2 - Day 1 and Day 15; Cycle 3 & subsequent cycles Day 1; end of study and follow-up 28 days after last dose.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	56	91	
Units: mmHg				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=52,51,73)	-4.3 (± 11.1)	-2.9 (± 9.2)	-1.8 (± 14.2)	
Cycle 1 Day 15 (n=56,56,91)	3.8 (± 12.2)	4.1 (± 12.5)	11.5 (± 18)	
Cycle 2 Day 1 (n=56,56,91)	1.9 (± 12.4)	0.9 (± 13.6)	9.9 (± 18.7)	
Cycle 2 Day 15 (n=55,55,86)	3.6 (± 13.8)	2.7 (± 16.6)	5.9 (± 20.3)	
Cycle 3 Day 1 (n=48,49,84)	3.5 (± 15.1)	8.4 (± 15.4)	5.2 (± 20.2)	
Cycle 4 Day 1 (n=45,48,79)	4.3 (± 12.7)	3.5 (± 13)	5.5 (± 18.2)	
End of treatment (n=35,44,51)	2.4 (± 17)	1.7 (± 14)	-2.8 (± 19)	
Follow-up (n=16,25,36)	-3.6 (± 16.9)	-0.4 (± 16.3)	-0.6 (± 16.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in diastolic blood pressure

End point title	Change from baseline in diastolic blood pressure[14]

End point description:

Value at respective visit minus value at baseline.

End point type	Secondary

End point timeframe:

At screening (D-14 to D-1); lead-in period: Cycle 1 - Day 1 and Day 15; Cycle 2 - Day 1 and Day 15; Cycle 3 & subsequent cycles Day 1; end of study and follow-up 28 days after last dose.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	56	91	
Units: mmHg				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=52,51,73)	-1.6 (± 8.2)	-2.6 (± 7.4)	0.5 (± 8.4)	
Cycle 1 Day 15 (n=56,56,91)	4.8 (± 8.5)	3 (± 7.7)	11.5 (± 10)	
Cycle 2 Day 1 (n=56,56,91)	4.2 (± 9)	3.5 (± 8)	10.5 (± 10.5)	
Cycle 2 Day 15 (n=55,55,86)	5.5 (± 10.5)	4.4 (± 10.7)	9.7 (± 11.3)	
Cycle 3 Day 1 (n=48,49,84)	6.6 (± 8.3)	5.9 (± 9.3)	9.1 (± 13.6)	
Cycle 4 Day 1 (n=45,48,79)	7.4 (± 8.2)	4.6 (± 8.5)	8.7 (± 11.8)	

End of treatment (n=35,44,51)	0.6 (± 10.8)	3.5 (± 6.3)	3 (± 10.5)	
Follow-up (n=16,25,36)	-4.5 (± 10.1)	-1.3 (± 8.5)	1.8 (± 9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of Circulating Endothelial Cells (CECs) in blood: cluster of differentiation (CD)146+/CD105+ at baseline

End point title	Comparison of Circulating Endothelial Cells (CECs) in blood: cluster of differentiation (CD)146+/CD105+ at baseline[15]

End point description:

CECs are noninvasive marker of vascular damage, remodeling, and dysfunction. Samples were collected and following proteins were analyzed: CD146+/CD105+ CECs, CD146+/CD105+ mean fluorescence intensity (MFI) platelet derived growth factor receptor (PDGFR)-beta, CD146+/CD105+ MFI phospho-PDGFR (pPDGFR)-beta, CD146+/CD105+ phospho-Vascular endothelial growth factor receptor (pVEGFR), CD146+/CD105+ MFI VEGFR. The ratio of plasma levels of the biomarkers at the selected time point vs baseline is reported.

End point type	Secondary

End point timeframe:

At baseline - Beginning of the lead-in period (Cycle 1 Day 1)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	22	20	
Units: Fluorescent Intensity Unit (FIU)				
arithmetic mean (standard deviation)				
Baseline CECs Count (n=17,22,20)	23584 (± 18213.1)	28544 (± 27694.4)	29663 (± 30651)	
Baseline MFI PDGFR-BETA (n=17,22,20)	346815 (± 179563)	455238 (± 238157)	327567 (± 167728)	
Baseline MFI pPDGFR-BETA (n=17,22,20)	401226 (± 195445)	395509 (± 136933)	397672 (± 193172)	
Baseline MFI pVEGFR (n=16,22,20)	456086 (± 290174)	436197 (± 128225)	398754 (± 188137)	
Baseline MFI VEGFR (n=16,22,20)	367799 (± 181320)	473290 (± 228619)	359092 (± 167706)	

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of the ratio of CECs in blood: CD146+/CD105+ at each time

point to baseline

End point title	Comparison of the ratio of CECs in blood: CD146+/CD105+ at each time point to baseline[16]

End point description:

CECs are noninvasive marker of vascular damage, remodeling, and dysfunction. Samples were collected and following proteins were analyzed: CD146+/CD105+ CECs, CD146+/CD105+ MFI platelet derived growth factor receptor (PDGFR)-beta, CD146+/CD105+ MFI phospho-PDGFR (pPDGFR)-beta, CD146+/CD105+ phospho-VEGFR (pVEGFR), CD146+/CD105+ MFI VEGFR. The ratio of plasma levels of the biomarkers at the selected time point vs baseline is reported.

End point type	Secondary

End point timeframe:

At end of the lead-in period (Cycle 1 Day 15), Cycle 2 Day 15 and End of therapy (EOT)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	22	20	
Units: Ratio				
arithmetic mean (standard deviation)				
C1D15:C1D1 CECs Count (n=11,18,14)	2.3 (± 2.52)	3.7 (± 6.92)	2.2 (± 3.1)	
C2D15:C1D1 CECs Count (n=13,16,11)	1.3 (± 1.43)	4.4 (± 9.27)	1.3 (± 1.22)	
EOT:C1D1 CECs Count (n=7,9,4)	2.8 (± 4.81)	8.9 (± 21.7)	1.2 (± 1.5)	
C1D15:C1D1 MFI PDGFRBETA (n=11,17,13)	1.3 (± 1.03)	1.5 (± 1.14)	1.1 (± 0.73)	
C2D15:C1D1 MFI PDGFRBETA (n=13,16,11)	1.4 (± 1.24)	1.1 (± 1.14)	1.62 (± 1.62)	
EOT:C1D1 MFI PDGFRBETA (n=7,9,4)	1.5 (± 1.75)	0.6 (± 0.52)	1.2 (± 1.78)	
C1D15:C1D1 MFI pPDGFR-BETA (n=11,17,13)	1.1 (± 0.63)	1.2 (± 0.77)	1 (± 1.12)	
C2D15:C1D1 MFI pPDGFR-BETA (n=13,16,11)	1 (± 0.69)	0.8 (± 0.45)	1.2 (± 0.79)	
EOT:C1D1 MFI pPDGFRBETA (n=7,9,4)	0.8 (± 0.71)	0.8 (± 0.93)	1.9 (± 1.57)	
C1D15:C1D1 MFI pVEGFR (n=10,18,14)	1 (± 0.46)	1.2 (± 0.88)	1.2 (± 1)	
C2D15:C1D1 MFI pVEGFR (n=12,16,11)	1 (± 0.74)	0.9 (± 0.82)	1.2 (± 0.8)	
EOT:C1D1 MFI pVEGFR (n=7,9,4)	0.8 (± 0.53)	1.3 (± 0.96)	3 (± 1.16)	
C1D15:C1D1 MFI VEGFR (n=10,18,14)	1.4 (± 1.25)	1.3 (± 0.94)	1 (± 0.64)	
C2D15:C1D1 MFI VEGFR (n=12,16,11)	1.5 (± 1.48)	1.3 (± 0.99)	2.1 (± 1.72)	
EOT:C1D1 MFI VEGFR (n=7,9,4)	1.1 (± 1.03)	0.7 (± 0.48)	1.9 (± 1.63)	

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating Endothelial Cells (CECs) in blood: CD31+/CD146+

End point title	Circulating Endothelial Cells (CECs) in blood:

End point description:

CECs are noninvasive marker of vascular damage, remodeling, and dysfunction. Samples were collected and following proteins were analyzed: CD31+/CD146+ CECs, CD31+/CD146+ MFI PDGFR-beta, CD31+/CD146+ MFI pPDGFR-beta, CD31+/CD146+ pVEGFR, CD31+/CD146+ MFI VEGFR. The ratio of plasma levels of the biomarkers at the selected time point vs baseline is reported.

End point type	Secondary

End point timeframe:

At baseline - Beginning of the lead-in period (Cycle 1 Day 1)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	22	20	
Units: Fluorescent Intensity Unit (FIU)				
arithmetic mean (standard deviation)				
Baseline CECs Count (n=17,22,20)	74668 (± 50558.9)	76258 (± 46779.5)	77437 (± 63419.4)	
Baseline MFI PDGFR-BETA (n=17,21,20)	333760 (± 164604)	380886 (± 147261)	442642 (± 267436)	
Baseline MFI pPDGFR-BETA (n=17,21,20)	380139 (± 205600)	355441 (± 147046)	383202 (± 211174)	
Baseline MFI pVEGFR (n=17,22,20)	385617 (± 203956)	352644 (± 128803)	380184 (± 173578)	
Baseline MFI VEGFR (n=17,22,20)	330333 (± 151710)	401909 (± 165235)	359097 (± 146943)	

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of ratio of CECs in blood: CD31+/CD146+ at each time point to baseline

End point title	Comparison of ratio of CECs in blood: CD31+/CD146+ at each time point to baseline[18]

End point description:

CECs are noninvasive marker of vascular damage, remodeling, and dysfunction. Samples were collected and following proteins were analyzed: CD31+/CD146+ CECs, CD31+/CD146+ MFI PDGFR-beta, CD31+/CD146+ MFI pPDGFR-beta, CD31+/CD146+ pVEGFR, CD31+/CD146+ MFI VEGFR. The ratio of plasma levels of the biomarkers at the selected time point vs baseline is reported.

End point type	Secondary

End point timeframe:

At end of the lead-in period (Cycle 1 Day 15), Cycle 2 Day 15 and End of therapy (EOT)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	22	20	
Units: Ratio				
arithmetic mean (standard deviation)				
C1D15:C1D1 CECs Count (n=11,18,14)	2.7 (± 3.17)	1.6 (± 2.32)	1.5 (± 2.31)	
C2D15:C1D1 CECs Count (n=13,16,11)	1.4 (± 1.4)	2.2 (± 3.91)	2.5 (± 3.98)	
EOT:C1D1 CECs COUNT (n=7,9,4)	1.5 (± 1.95)	1.4 (± 2.2)	0.6 (± 0.71)	
C1D15:C1D1 MFI PDGFRBETA (n=11,15,13)	1.2 (± 0.74)	1.3 (± 0.89)	0.8 (± 0.51)	
C2D15:C1D1 MFI PDGFRBETA (n=13,14,11)	1.4 (± 1.36)	1.1 (± 1.03)	2.2 (± 2.64)	
EOT:C1D1 MFI PDGFRBETA (n=6,8,4)	1.2 (± 1.23)	0.6 (± 0.51)	1.7 (± 1.49)	
C1D15:C1D1 MFI pPDGFR-BETA (n=11,15,13)	1.2 (± 1.07)	1.4 (± 0.81)	1 (± 0.87)	
C2D15:C1D1 MFI pPDGFR-BETA (n=13,14,11)	1.2 (± 0.89)	0.8 (± 0.38)	1.1 (± 0.71)	
EOT:C1D1 MFI pPDGFRBETA (n=6,8,4)	0.7 (± 0.63)	0.8 (± 0.91)	3 (± 0.47)	
C1D15:C1D1 MFI pVEGFR (n=11,18,14)	1.1 (± 0.75)	1.4 (± 0.74)	1.2 (± 0.9)	
C2D15:C1D1 MFI pVEGFR (n=13,16,10)	1.2 (± 1)	0.9 (± 0.68)	1.3 (± 0.7)	
EOT:C1D1 MFI pVEGFR (n=7,9,4)	0.7 (± 0.59)	1.1 (± 1.24)	3.1 (± 0.95)	
C1D15:C1D1 MFI VEGFR (n=11,18,14)	1.3 (± 0.93)	1.3 (± 0.9)	1 (± 0.57)	
C2D15:C1D1 MFI VEGFR n=13,16,10)	1.5 (± 1.44)	1.2 (± 0.96)	2.1 (± 1.8)	
EOT:C1D1 MFI VEGFR (n=7,9,4)	1.2 (± 1.27)	1.1 (± 0.9)	1.5 (± 1.42)	

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in Subgroups That Were Defined by Vascular endothelial growth factor A (VEGFA) or Vascular endothelial growth factor receptor 3 (VEGFR3) Polymorphisms

End point title	ORR in Subgroups That Were Defined by Vascular endothelial growth factor A (VEGFA) or Vascular endothelial growth factor receptor 3 (VEGFR3) Polymorphisms[19]

End point description:

ORR, defined as proportion of participants with CR or PR according to RECIST, in subgroups that were defined by VEGFA or VEGFR3 polymorphisms.

End point type	Secondary

End point timeframe:

Baseline - Beginning of the lead-in period (Cycle 1 Day 1)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	49	79	
Units: Percentage of participants				
number (confidence interval 95%)				
VEGFA/rs699947 Genotype: A/A (n = 7, 9, 14)	85.7 (42.1 to 99.6)	22.2 (2.8 to 60)	42.9 (17.7 to 71.1)	
VEGFA/rs699947 Genotype: A/C (n = 22, 20, 41)	54.5 (32.2 to 75.6)	35 (15.4 to 59.2)	65.9 (49.4 to 79.9)	
VEGFA/rs699947 Genotype: C/C (n = 14, 14, 24)	50 (23 to 77)	35.7 (12.8 to 64.9)	66.7 (44.7 to 84.4)	
VEGFA/rs1570360 Genotype: G/G (n = 22, 23, 43)	59.1 (36.4 to 79.3)	39.1 (19.7 to 61.5)	67.4 (51.5 to 80.9)	
VEGFA/rs1570360 Genotype: G/A (n = 19, 16, 29)	57.9 (33.5 to 79.7)	18.8 (4 to 45.6)	58.6 (38.9 to 76.5)	
VEGFA/rs1570360 Genotype: A/A (n = 2, 4, 7)	50 (1.3 to 98.7)	50 (6.8 to 93.2)	42.9 (9.9 to 81.6)	
VEGFR3/rs448012 Genotype: G/G (n = 16, 15, 28)	81.3 (54.4 to 96)	53.3 (26.6 to 78.7)	60.7 (40.6 to 78.5)	
VEGFR3/rs448012 Genotype: G/C (n = 22, 22, 35)	45.5 (24.4 to 67.8)	18.2 (5.2 to 40.3)	57.1 (39.4 to 73.7)	
VEGFR3/rs448012 Genotype: C/C (n = 5, 6, 16)	40 (5.3 to 85.3)	33.3 (4.3 to 77.7)	75 (47.6 to 92.7)	
VEGFR3/rs307826 Genotype: A/A (n = 36, 39, 79)	58.3 (40.8 to 74.5)	30.8 (17 to 47.6)	64.3 (51.9 to 75.4)	
VEGFR3/rs307826 Genotype: A/G (n = 6, 4, 9)	50 (11.8 to 88.2)	50 (6.8 to 93.2)	44.4 (13.7 to 78.8)	
VEGFR3/rs307826 Genotype: G/G (n = 1, 0, 0)	100 (2.5 to 100)	0 (0 to 0)	0 (0 to 0)	
VEGFR3/rs307821 Genotype: G/G (n = 36, 38, 79)	55.6 (38.1 to 72.1)	28.9 (15.4 to 45.9)	65.2 (52.8 to 76.3)	
VEGFR3/rs307821 Genotype: G/T (n = 6, 5, 10)	66.7 (22.3 to 95.7)	60 (14.7 to 94.7)	40 (12.2 to 73.8)	
VEGFR3/rs307821 Genotype: T/T (n = 1, 0, 0)	100 (2.5 to 100)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in Subgroups That Were Defined by Vascular endothelial growth factor A (VEGFA) or Vascular endothelial growth factor receptor 3 (VEGFR3) Polymorphisms

End point title	PFS in Subgroups That Were Defined by Vascular endothelial growth factor A (VEGFA) or Vascular endothelial growth factor receptor 3 (VEGFR3) Polymorphisms[20]

End point description:

PFS, defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause, in subgroups that were defined by VEGFA or VEGFR3 polymorphisms. Estimates of the PFS curves from the Kaplan-Meier method were presented.

End point type	Secondary

End point timeframe:

Baseline - Beginning of the lead-in period (Cycle 1 Day 1)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analyses have been specified for this end point. No inferential statistical analysis was done.

End point values	Active Titration Arm	Placebo Titration Arm	Non-randomized Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	43	79	
Units: Months				
median (confidence interval 95%)				
VEGFA/rs699947 Genotype: A/A (n = 7, 9, 14)	9999 (1.74 to 9999)	11.5 (7.33 to 9999)	7.33 (5.06 to 13.83)	
VEGFA/rs699947 Genotype: A/C (n = 22, 20, 41)	11.07 (3.02 to 17.44)	9.67 (1.91 to 16.59)	16.59 (10.97 to 9999)	
VEGFA/rs699947 Genotype: C/C (n = 14, 14, 41)	18.74 (1.84 to 9999)	24.64 (4.01 to 9999)	25.13 (8.28 to 30.45)	
VEGFA/rs1570360 Genotype: G/G (n = 22, 23, 43)	14.62 (7.39 to 9999)	19.42 (5.81 to 27.63)	25.13 (11.47 to 30.45)	
VEGFA/rs1570360 Genotype: G/A (n = 19, 16, 29)	12.78 (1.84 to 9999)	8.34 (1.91 to 16.59)	13.9 (8.28 to 22.54)	
VEGFA/rs1570360 Genotype: A/A (n = 2, 4, 29)	9999 (1.74 to 9999)	10.04 (3.58 to 9999)	8.57 (1.74 to 9999)	
VEGFR3/rs448012 Genotype: G/G (n = 16, 15, 28)	17.44 (12.78 to 9999)	19.42 (5.35 to 9999)	22.54 (8.08 to 9999)	
VEGFR3/rs448012 Genotype: G/C (n = 22, 22, 35)	9.18 (1.84 to 9999)	8.31 (3.58 to 16.52)	13.83 (5.62 to 16.59)	
VEGFR3/rs448012 Genotype: C/C (n = 5, 6, 16)	11.07 (1.84 to 9999)	15.67 (1.91 to 27.63)	9999 (8.57 to 9999)	
VEGFR3/rs307826 Genotype: A/A (n = 36, 39, 70)	13.73 (8.28 to 24.47)	15.67 (8.21 to 22.17)	16.56 (10.28 to 25.13)	
VEGFR3/rs307826 Genotype: A/G (n = 6, 4, 9)	16.52 (1.18 to 9999)	7.93 (1.84 to 11.86)	16.26 (2.66 to 30.45)	
VEGFR3/rs307826 Genotype: G/G (n = 0, 0, 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
VEGFR3/rs307821 Genotype: G/G (n = 36, 38, 69)	12.78 (7.39 to 24.47)	15.67 (8.21 to 23.95)	16.59 (10.28 to 28.52)	
VEGFR3/rs307821 Genotype: G/T (n = 36, 38, 10)	24.8 (1.18 to 9999)	8.34 (1.84 to 11.86)	13.86 (2.66 to 30.45)	
VEGFR3/rs307821 Genotype: T/T (n = 1, 0, 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 years

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Active Titration Arm

Reporting group description:

Participants initially received axitinib 5 mg twice a day (BID) + axitinib(blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + axitinib (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + axitinib [blinded therapy] 5 mg BID).

Reporting group title	Non-randomized Arm

Reporting group description:

Participants not eligible for randomization were assigned to receive axitinib 5 mg BID or a reduced dose per the dose modification guideline. Dose titration was not permitted in this treatment arm.

Reporting group title	Placebo Titration Arm

Reporting group description:

Participants initially received axitinib 5mg BID + placebo (blinded therapy) 2 mg BID. After at least 2 consecutive weeks, participants satisfying the dose titration criteria had their dose level increased by one additional dose level, to axitinib 5 mg BID + placebo (blinded therapy) 5 mg BID, unless otherwise contraindicated per the investigator's clinical judgment. The maximum total daily dose was 10 mg BID (axitinib 5mg BID + placebo [blinded therapy] 5 mg BID).

Reporting group title	Discontinued Prior to Randomization

Reporting group description:

Participants who were discontinued prior to randomization to either treatment or non-randomization arms.

Serious adverse events	Active Titration Arm	Non-randomized Arm	Placebo Titration Arm
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 56 (44.64%)	39 / 91 (42.86%)	14 / 56 (25.00%)
number of deaths (all causes)	4	0	1
number of deaths resulting from adverse events	3	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Breast cancer			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Surgical and medical procedures			
Incisional hernia repair			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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

General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 56 (1.79%)	6 / 91 (6.59%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
General physical health deterioration			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 56 (1.79%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	2 / 56 (3.57%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic prolapse			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Hypercapnia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Pulmonary embolism			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Blood creatinine increased			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood sodium decreased			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Postoperative hernia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Postoperative wound complication			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Road traffic accident			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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

Incisional hernia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 56 (1.79%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 56 (0.00%)	2 / 91 (2.20%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diastolic dysfunction			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	4 / 56 (7.14%)	2 / 91 (2.20%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Coronary artery disease			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Nervous system disorders			
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoparesis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 56 (0.00%)	3 / 91 (3.30%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 56 (3.57%)	1 / 91 (1.10%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	3 / 3	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 56 (3.57%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 56 (5.36%)	1 / 91 (1.10%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	3 / 4	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 56 (1.79%)	1 / 91 (1.10%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain upper			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	2 / 56 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn’s disease			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Enterocolitis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Ileus			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Intestinal obstruction			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary colic			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Cholelithiasis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postrenal failure			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Renal failure			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute kidney injury			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Urinary retention			
subjects affected / exposed	0 / 56 (0.00%)	2 / 91 (2.20%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 56 (3.57%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			

subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 56 (5.36%)	1 / 91 (1.10%)	2 / 56 (3.57%)
occurrences causally related to treatment / all	3 / 5	0 / 2	0 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Lung infection			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Osteomyelitis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (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
Postoperative wound infection			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingivitis			

subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	5 / 56 (8.93%)	3 / 91 (3.30%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	3 / 7	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 56 (1.79%)	2 / 91 (2.20%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 1	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Discontinued Prior to Randomization		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			

subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colon cancer				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Circulatory collapse				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				

Incisional hernia repair			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic prolapse			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			

subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercapnia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Delirium				

subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood sodium decreased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative hernia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative wound complication			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cervical vertebral fracture				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incisional hernia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative ileus				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Myocardial ischaemia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diastolic dysfunction				

subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute coronary syndrome				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular insufficiency				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				

subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Monoparesis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Neutropenia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaemia				

subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Abdominal pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Crohn’s disease				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal hypomotility				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				

subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Biliary colic			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postrenal failure			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal failure				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Hypothyroidism				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemarthrosis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cystitis				

subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung abscess				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis bacterial				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				

subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gingivitis				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Active Titration Arm	Non-randomized Arm	Placebo Titration Arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 56 (98.21%)	91 / 91 (100.00%)	51 / 56 (91.07%)
Vascular disorders			
Hypertension			
subjects affected / exposed	35 / 56 (62.50%)	76 / 91 (83.52%)	24 / 56 (42.86%)
occurrences (all)	67	167	75
Hypotension			
subjects affected / exposed	0 / 56 (0.00%)	9 / 91 (9.89%)	8 / 56 (14.29%)
occurrences (all)	0	10	11
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	3 / 56 (5.36%)
occurrences (all)	0	1	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 56 (10.71%)	6 / 91 (6.59%)	5 / 56 (8.93%)
occurrences (all)	9	11	7
Fatigue			
subjects affected / exposed	27 / 56 (48.21%)	49 / 91 (53.85%)	26 / 56 (46.43%)
occurrences (all)	74	127	66
General physical health deterioration			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	12 / 56 (21.43%)	13 / 91 (14.29%)	8 / 56 (14.29%)
occurrences (all)	21	39	21
Chest pain			
subjects affected / exposed	5 / 56 (8.93%)	6 / 91 (6.59%)	2 / 56 (3.57%)
occurrences (all)	8	6	2
Chills			
subjects affected / exposed	4 / 56 (7.14%)	5 / 91 (5.49%)	1 / 56 (1.79%)
occurrences (all)	4	5	1
Oedema peripheral			
subjects affected / exposed	4 / 56 (7.14%)	14 / 91 (15.38%)	3 / 56 (5.36%)
occurrences (all)	11	29	3

Pain			
subjects affected / exposed	4 / 56 (7.14%)	6 / 91 (6.59%)	3 / 56 (5.36%)
occurrences (all)	5	9	3
Pyrexia			
subjects affected / exposed	6 / 56 (10.71%)	4 / 91 (4.40%)	3 / 56 (5.36%)
occurrences (all)	8	4	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 56 (12.50%)	19 / 91 (20.88%)	8 / 56 (14.29%)
occurrences (all)	8	25	13
Dysphonia			
subjects affected / exposed	18 / 56 (32.14%)	44 / 91 (48.35%)	20 / 56 (35.71%)
occurrences (all)	27	74	20
Dyspnoea			
subjects affected / exposed	6 / 56 (10.71%)	27 / 91 (29.67%)	8 / 56 (14.29%)
occurrences (all)	15	36	11
Epistaxis			
subjects affected / exposed	4 / 56 (7.14%)	12 / 91 (13.19%)	3 / 56 (5.36%)
occurrences (all)	5	24	3
Oropharyngeal pain			
subjects affected / exposed	4 / 56 (7.14%)	8 / 91 (8.79%)	2 / 56 (3.57%)
occurrences (all)	5	9	2
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 56 (1.79%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences (all)	1	0	1
Insomnia			
subjects affected / exposed	3 / 56 (5.36%)	8 / 91 (8.79%)	4 / 56 (7.14%)
occurrences (all)	4	10	4
Anxiety			
subjects affected / exposed	3 / 56 (5.36%)	7 / 91 (7.69%)	3 / 56 (5.36%)
occurrences (all)	4	10	3
Depression			
subjects affected / exposed	4 / 56 (7.14%)	6 / 91 (6.59%)	4 / 56 (7.14%)
occurrences (all)	5	8	4
Delirium			

subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 56 (10.71%)	12 / 91 (13.19%)	9 / 56 (16.07%)
occurrences (all)	10	36	21
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 56 (10.71%)	12 / 91 (13.19%)	10 / 56 (17.86%)
occurrences (all)	10	36	23
Blood creatinine increased			
subjects affected / exposed	4 / 56 (7.14%)	14 / 91 (15.38%)	8 / 56 (14.29%)
occurrences (all)	10	31	17
Blood glucose increased			
subjects affected / exposed	4 / 56 (7.14%)	10 / 91 (10.99%)	7 / 56 (12.50%)
occurrences (all)	24	23	17
Fibrin D dimer increased			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	2
Weight decreased			
subjects affected / exposed	16 / 56 (28.57%)	25 / 91 (27.47%)	12 / 56 (21.43%)
occurrences (all)	53	88	22
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 56 (7.14%)	6 / 91 (6.59%)	4 / 56 (7.14%)
occurrences (all)	4	12	5
Blood glucose decreased			
subjects affected / exposed	3 / 56 (5.36%)	1 / 91 (1.10%)	5 / 56 (8.93%)
occurrences (all)	10	1	7
Blood potassium increased			
subjects affected / exposed	4 / 56 (7.14%)	4 / 91 (4.40%)	3 / 56 (5.36%)
occurrences (all)	30	5	17
Blood triglycerides increased			
subjects affected / exposed	2 / 56 (3.57%)	5 / 91 (5.49%)	2 / 56 (3.57%)
occurrences (all)	3	17	3
Haemoglobin decreased			

subjects affected / exposed	1 / 56 (1.79%)	5 / 91 (5.49%)	1 / 56 (1.79%)
occurrences (all)	1	14	6
Blood albumin decreased			
subjects affected / exposed	1 / 56 (1.79%)	1 / 91 (1.10%)	3 / 56 (5.36%)
occurrences (all)	1	8	4
Blood sodium decreased			
subjects affected / exposed	2 / 56 (3.57%)	1 / 91 (1.10%)	3 / 56 (5.36%)
occurrences (all)	4	2	5
Blood thyroid stimulating hormone increased			
subjects affected / exposed	8 / 56 (14.29%)	9 / 91 (9.89%)	7 / 56 (12.50%)
occurrences (all)	34	15	10
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	9 / 56 (16.07%)	21 / 91 (23.08%)	5 / 56 (8.93%)
occurrences (all)	15	31	10
Dyskinesia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 91 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	9 / 56 (16.07%)	27 / 91 (29.67%)	15 / 56 (26.79%)
occurrences (all)	18	53	25
Hypoaesthesia			
subjects affected / exposed	2 / 56 (3.57%)	4 / 91 (4.40%)	0 / 56 (0.00%)
occurrences (all)	2	5	0
Paraesthesia			
subjects affected / exposed	5 / 56 (8.93%)	3 / 91 (3.30%)	3 / 56 (5.36%)
occurrences (all)	8	3	4
Transient ischaemic attack			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Dizziness			

subjects affected / exposed	8 / 56 (14.29%)	14 / 91 (15.38%)	10 / 56 (17.86%)
occurrences (all)	14	53	16
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 56 (7.14%)	3 / 91 (3.30%)	1 / 56 (1.79%)
occurrences (all)	6	4	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 56 (8.93%)	9 / 91 (9.89%)	4 / 56 (7.14%)
occurrences (all)	5	13	6
Lymphopenia			
subjects affected / exposed	0 / 56 (0.00%)	2 / 91 (2.20%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	5 / 56 (8.93%)	15 / 91 (16.48%)	3 / 56 (5.36%)
occurrences (all)	8	22	5
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 56 (0.00%)	4 / 91 (4.40%)	3 / 56 (5.36%)
occurrences (all)	0	4	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 56 (16.07%)	11 / 91 (12.09%)	9 / 56 (16.07%)
occurrences (all)	26	17	10
Abdominal pain upper			
subjects affected / exposed	6 / 56 (10.71%)	11 / 91 (12.09%)	2 / 56 (3.57%)
occurrences (all)	9	14	2
Constipation			
subjects affected / exposed	11 / 56 (19.64%)	27 / 91 (29.67%)	7 / 56 (12.50%)
occurrences (all)	15	43	11
Diarrhoea			
subjects affected / exposed	34 / 56 (60.71%)	58 / 91 (63.74%)	35 / 56 (62.50%)
occurrences (all)	232	236	97
Dry Mouth			
subjects affected / exposed	7 / 56 (12.50%)	7 / 91 (7.69%)	2 / 56 (3.57%)
occurrences (all)	9	8	2
Dyspepsia			

subjects affected / exposed	7 / 56 (12.50%)	18 / 91 (19.78%)	5 / 56 (8.93%)
occurrences (all)	10	24	5
Dysphagia			
subjects affected / exposed	0 / 56 (0.00%)	2 / 91 (2.20%)	2 / 56 (3.57%)
occurrences (all)	0	3	2
Flatulence			
subjects affected / exposed	7 / 56 (12.50%)	4 / 91 (4.40%)	3 / 56 (5.36%)
occurrences (all)	7	7	3
Haemorrhoids			
subjects affected / exposed	2 / 56 (3.57%)	4 / 91 (4.40%)	1 / 56 (1.79%)
occurrences (all)	2	8	1
Nausea			
subjects affected / exposed	24 / 56 (42.86%)	33 / 91 (36.26%)	19 / 56 (33.93%)
occurrences (all)	70	66	57
Stomatitis			
subjects affected / exposed	10 / 56 (17.86%)	17 / 91 (18.68%)	4 / 56 (7.14%)
occurrences (all)	18	26	4
Vomiting			
subjects affected / exposed	18 / 56 (32.14%)	25 / 91 (27.47%)	12 / 56 (21.43%)
occurrences (all)	35	44	37
Abdominal discomfort			
subjects affected / exposed	2 / 56 (3.57%)	6 / 91 (6.59%)	0 / 56 (0.00%)
occurrences (all)	2	9	2
Abdominal distension			
subjects affected / exposed	1 / 56 (1.79%)	3 / 91 (3.30%)	3 / 56 (5.36%)
occurrences (all)	1	5	3
Gastritis			
subjects affected / exposed	3 / 56 (5.36%)	9 / 91 (9.89%)	2 / 56 (3.57%)
occurrences (all)	3	13	3
Toothache			
subjects affected / exposed	1 / 56 (1.79%)	5 / 91 (5.49%)	3 / 56 (5.36%)
occurrences (all)	1	16	5
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 56 (3.57%)	6 / 91 (6.59%)	3 / 56 (5.36%)
occurrences (all)	2	6	3
Proctalgia			

subjects affected / exposed	2 / 56 (3.57%)	5 / 91 (5.49%)	0 / 56 (0.00%)
occurrences (all)	2	7	0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	3 / 56 (5.36%)	5 / 91 (5.49%)	1 / 56 (1.79%)
occurrences (all)	4	9	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	7 / 56 (12.50%)	7 / 91 (7.69%)	3 / 56 (5.36%)
occurrences (all)	7	8	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	18 / 56 (32.14%)	40 / 91 (43.96%)	10 / 56 (17.86%)
occurrences (all)	37	199	45
Pruritus			
subjects affected / exposed	2 / 56 (3.57%)	13 / 91 (14.29%)	6 / 56 (10.71%)
occurrences (all)	7	16	9
Rash			
subjects affected / exposed	5 / 56 (8.93%)	19 / 91 (20.88%)	8 / 56 (14.29%)
occurrences (all)	8	30	11
Alopecia			
subjects affected / exposed	2 / 56 (3.57%)	14 / 91 (15.38%)	3 / 56 (5.36%)
occurrences (all)	2	14	3
Erythema			
subjects affected / exposed	1 / 56 (1.79%)	6 / 91 (6.59%)	2 / 56 (3.57%)
occurrences (all)	1	6	2
Hyperkeratosis			
subjects affected / exposed	2 / 56 (3.57%)	5 / 91 (5.49%)	4 / 56 (7.14%)
occurrences (all)	2	8	5
Renal and urinary disorders			
Haemoglobinuria			
subjects affected / exposed	2 / 56 (3.57%)	5 / 91 (5.49%)	3 / 56 (5.36%)
occurrences (all)	3	6	4
Proteinuria			
subjects affected / exposed	12 / 56 (21.43%)	40 / 91 (43.96%)	12 / 56 (21.43%)
occurrences (all)	41	376	43
Dysuria			

subjects affected / exposed	3 / 56 (5.36%)	3 / 91 (3.30%)	0 / 56 (0.00%)
occurrences (all)	5	5	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	18 / 56 (32.14%)	41 / 91 (45.05%)	13 / 56 (23.21%)
occurrences (all)	26	64	15
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 56 (23.21%)	17 / 91 (18.68%)	11 / 56 (19.64%)
occurrences (all)	23	33	53
Back pain			
subjects affected / exposed	13 / 56 (23.21%)	17 / 91 (18.68%)	8 / 56 (14.29%)
occurrences (all)	32	28	12
Groin pain			
subjects affected / exposed	0 / 56 (0.00%)	1 / 91 (1.10%)	0 / 56 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal pain			
subjects affected / exposed	8 / 56 (14.29%)	15 / 91 (16.48%)	4 / 56 (7.14%)
occurrences (all)	8	17	6
Bone pain			
subjects affected / exposed	3 / 56 (5.36%)	5 / 91 (5.49%)	2 / 56 (3.57%)
occurrences (all)	3	7	2
Flank pain			
subjects affected / exposed	1 / 56 (1.79%)	4 / 91 (4.40%)	3 / 56 (5.36%)
occurrences (all)	1	4	3
Muscle spasms			
subjects affected / exposed	3 / 56 (5.36%)	6 / 91 (6.59%)	3 / 56 (5.36%)
occurrences (all)	4	23	3
Muscular weakness			
subjects affected / exposed	3 / 56 (5.36%)	2 / 91 (2.20%)	2 / 56 (3.57%)
occurrences (all)	4	2	2
Musculoskeletal chest pain			
subjects affected / exposed	8 / 56 (14.29%)	15 / 91 (16.48%)	4 / 56 (7.14%)
occurrences (all)	8	17	6
Musculoskeletal stiffness			

subjects affected / exposed	1 / 56 (1.79%)	3 / 91 (3.30%)	4 / 56 (7.14%)
occurrences (all)	1	4	13
Myalgia			
subjects affected / exposed	4 / 56 (7.14%)	8 / 91 (8.79%)	3 / 56 (5.36%)
occurrences (all)	6	17	34
Neck pain			
subjects affected / exposed	4 / 56 (7.14%)	5 / 91 (5.49%)	4 / 56 (7.14%)
occurrences (all)	10	8	5
Pain in extremity			
subjects affected / exposed	8 / 56 (14.29%)	23 / 91 (25.27%)	9 / 56 (16.07%)
occurrences (all)	11	26	13
Infections and infestations			
Rhinitis			
subjects affected / exposed	3 / 56 (5.36%)	4 / 91 (4.40%)	6 / 56 (10.71%)
occurrences (all)	7	5	6
Urinary tract infection			
subjects affected / exposed	3 / 56 (5.36%)	10 / 91 (10.99%)	1 / 56 (1.79%)
occurrences (all)	6	20	1
Nasopharyngitis			
subjects affected / exposed	4 / 56 (7.14%)	19 / 91 (20.88%)	3 / 56 (5.36%)
occurrences (all)	8	37	6
Sinusitis			
subjects affected / exposed	4 / 56 (7.14%)	2 / 91 (2.20%)	2 / 56 (3.57%)
occurrences (all)	8	2	3
Upper respiratory tract infection			
subjects affected / exposed	4 / 56 (7.14%)	6 / 91 (6.59%)	3 / 56 (5.36%)
occurrences (all)	6	6	4
Respiratory tract infection			
subjects affected / exposed	2 / 56 (3.57%)	0 / 91 (0.00%)	3 / 56 (5.36%)
occurrences (all)	2	0	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 56 (37.50%)	37 / 91 (40.66%)	16 / 56 (28.57%)
occurrences (all)	45	109	28
Dehydration			

subjects affected / exposed	3 / 56 (5.36%)	5 / 91 (5.49%)	4 / 56 (7.14%)
occurrences (all)	3	8	6
Hyponatraemia			
subjects affected / exposed	4 / 56 (7.14%)	4 / 91 (4.40%)	1 / 56 (1.79%)
occurrences (all)	6	9	2
Hyperglycaemia			
subjects affected / exposed	4 / 56 (7.14%)	6 / 91 (6.59%)	3 / 56 (5.36%)
occurrences (all)	4	8	7
Hyperkalaemia			
subjects affected / exposed	6 / 56 (10.71%)	5 / 91 (5.49%)	1 / 56 (1.79%)
occurrences (all)	7	6	1
Hyperlipidaemia			
subjects affected / exposed	0 / 56 (0.00%)	7 / 91 (7.69%)	0 / 56 (0.00%)
occurrences (all)	0	12	0
Hyperuricaemia			
subjects affected / exposed	1 / 56 (1.79%)	9 / 91 (9.89%)	0 / 56 (0.00%)
occurrences (all)	1	17	0
Hypoalbuminaemia			
subjects affected / exposed	3 / 56 (5.36%)	2 / 91 (2.20%)	1 / 56 (1.79%)
occurrences (all)	7	4	1
Hypoglycaemia			
subjects affected / exposed	0 / 56 (0.00%)	2 / 91 (2.20%)	3 / 56 (5.36%)
occurrences (all)	0	2	3
Hypophosphataemia			
subjects affected / exposed	2 / 56 (3.57%)	4 / 91 (4.40%)	2 / 56 (3.57%)
occurrences (all)	2	15	3

Non-serious adverse events	Discontinued Prior to Randomization		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	12		
Hypotension			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	7		
General physical health deterioration			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Dysphonia subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3		
Epistaxis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Psychiatric disorders Confusional state subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Insomnia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Anxiety subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Depression subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Delirium subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood creatinine increased				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Blood glucose increased				
subjects affected / exposed	2 / 10 (20.00%)			
occurrences (all)	3			
Fibrin D dimer increased				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Weight decreased				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Blood alkaline phosphatase increased				
subjects affected / exposed	2 / 10 (20.00%)			
occurrences (all)	2			
Blood glucose decreased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood potassium increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood triglycerides increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Haemoglobin decreased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood albumin decreased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood sodium decreased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood thyroid stimulating hormone				

increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dyskinesia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Transient ischaemic attack			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Lymphopenia			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dry Mouth			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Dysphagia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Haemorrhoids			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	4		
Stomatitis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Abdominal discomfort			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Proctalgia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dry skin			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hyperkeratosis			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Haemoglobinuria			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			

Arthralgia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Back pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Groin pain				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Musculoskeletal pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Bone pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Flank pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Muscle spasms				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Muscular weakness				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Musculoskeletal chest pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Musculoskeletal stiffness				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Myalgia				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Neck pain				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			

Pain in extremity subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 4		
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Sinusitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3		
Dehydration subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Hyponatraemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Hyperkalaemia			

subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hyperlipidaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported