Clinical trial results:
Axitinib (AG-013736) As Second Line Therapy For Metastatic Renal Cell Cancer: Axis Trial

Summary

EudraCT number	2008-001451-21
Trial protocol	SE ES AT FR GB IE DE IT PL GR SK
Global end of trial date	25 February 2016

Results information

Result version number	v1 (current)
This version publication date	16 March 2017
First version publication date	16 March 2017
Summary attachment (see zip file)	A4061032 EU Posting (A4061032 PDS.pdf)

Trial information

Trial identification

Sponsor protocol code	A4061032

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00678392
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, 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	09 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the progression-free survival (PFS) of subjects with mRCC receiving AG-013736 vs sorafenib following failure of one prior systemic first-line regimen containing one or more of the following: sunitinib, bevacizumab + IFN alpha, temsirolimus, or cytokine(s).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Brazil: 17
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	China: 26
Country: Number of subjects enrolled	France: 67
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	India: 23
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Japan: 54
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	Russian Federation: 81
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Sweden: 3

Country: Number of subjects enrolled	Taiwan: 20
Country: Number of subjects enrolled	United Kingdom: 48
Country: Number of subjects enrolled	United States: 169
Worldwide total number of subjects	723
EEA total number of subjects	276

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)	476
From 65 to 84 years	247
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted at multiple sites in United Kingdom. Study started on 03 September 2008 and completed on 25 February 2016.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Axitinib 5 mg

Arm description:

Axitinib (AG-013736) 5 milligram (mg) tablet administered orally twice daily in cycles of 4 weeks.

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

Dosage and administration details:

Subjects received Axitinib (AG-013736) 5 mg tablet orally twice daily in cycles of 4 weeks.

Arm title	Sorafenib 400 mg

Arm description:

Sorafenib 400 mg tablet administered orally twice daily in cycles of 4 weeks.

Arm type	Active comparator
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Sorafenib 400 mg tablet orally twice daily in cycles of 4 weeks.

Number of subjects in period 1	Axitinib 5 mg	Sorafenib 400 mg
Started	361	362
Completed	0	0
Not completed	361	362
Consent withdrawn by subject	4	4
Adverse Event	-	6

Objective Progression or Relapse	3	8
Death	280	269
Sponsor Decision	1	2
Randomized But Not Treated	2	7
Unspecified	56	53
Lost to follow-up	15	13

Baseline characteristics

Reporting groups	
Reporting group title	Axitinib 5 mg
Reporting group description:	
Axitinib (AG-013736) 5 milligram (mg) tablet administered orally twice daily in cycles of 4 weeks.	
Reporting group title	Sorafenib 400 mg
Reporting group description:	
Sorafenib 400 mg tablet administered orally twice daily in cycles of 4 weeks.	

Reporting group values	Axitinib 5 mg	Sorafenib 400 mg	Total
Number of subjects	361	362	723
Age Categorical Units: Subjects			
Adults (18-64 years)	238	238	476
From 65-84 years	123	124	247
Age Continuous Units: years			
arithmetic mean	59.7	60	
standard deviation	± 10.5	± 10.1	-
Gender Categorical Units: Subjects			
Female	96	104	200
Male	265	258	523

End points

End points reporting groups	
Reporting group title	Axitinib 5 mg
Reporting group description:	
Axitinib (AG-013736) 5 milligram (mg) tablet administered orally twice daily in cycles of 4 weeks.	
Reporting group title	Sorafenib 400 mg
Reporting group description:	
Sorafenib 400 mg tablet administered orally twice daily in cycles of 4 weeks.	

Primary: Progression-Free Survival (PFS)	
End point title	Progression-Free Survival (PFS)
End point description:	
PFS was defined as the time in months from start of study treatment to the first documentation of objective tumor progression of disease (PD) or to death due to any cause, whichever occurs first. PD was assessed by response evaluation criteria in solid tumors (RECIST) version 1.0. PD = greater than or equal to (>=) 20 percent (%) increase in the sum of the longest dimensions (LD) of the target lesions taking as a reference the smallest sum of the LD recorded since the start of treatment or unequivocal progression in non-target lesions or the appearance of 1 or more new lesions. Occurrence of a pleural effusion or ascites was also considered PD if demonstrated by cytological investigation and it was not previously documented. New bone lesions not previously documented were considered PD if confirmed by computed tomography/magnetic resonance imaging or X-ray. Full analysis set (FAS).	
End point type	Primary
End point timeframe:	
From initiation of treatment up to follow-up period (up to 3 years)	

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	362		
Units: Months				
median (confidence interval 95%)	6.7 (6.3 to 8.6)	4.7 (4.6 to 5.6)		

Statistical analyses

Statistical analysis title	Axitinib vs Sorafenib
Comparison groups	Sorafenib 400 mg v Axitinib 5 mg
Number of subjects included in analysis	723
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.665

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.544
upper limit	0.812

Notes:

[1] - P-value was obtained from 1-sided log rank test, stratified by eastern cooperative oncology group (ECOG) and prior treatment. One-sided log-rank test at 0.025 level of significance was used to compare PFS between the 2 treatment arms.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the duration from start of study treatment to date of death due to any cause. OS was calculated as (months) = (date of death minus the date of first dose of study medication plus 1) divided by 30.4. For subjects who were alive, overall survival was censored on last date the subjects were known to be alive. FAS included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or receive a different drug from that to which they were randomized.

End point type	Secondary

End point timeframe:

From initiation of treatment up to follow-up period (up to 3 years)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	362		
Units: Months				
median (confidence interval 95%)	20.1 (16.7 to 23.4)	19.2 (17.5 to 22.3)		

Statistical analyses

Statistical analysis title	Axitinib vs Sorafenib
Comparison groups	Axitinib 5 mg v Sorafenib 400 mg
Number of subjects included in analysis	723
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3744 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.969
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.174

Notes:

[2] - P-value was obtained from a 1-sided log-rank test of treatment stratified by ECOG performance status and prior treatment.

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR = percentage of subjects with confirmed complete response (CR) or confirmed partial response (PR) according to the RECIST version 1.0 recorded from first dose of study treatment until PD or death due to any cause. CR: disappearance of all target, non target lesions and no appearance of new lesions, documented on 2 occasions separated by at least 4 weeks. PR: at least 30 % decrease in sum of LD of target lesions taking as reference baseline sum of LD, without progression of non target lesions, no appearance of new lesions. PD: >=20% increase in sum of LD of the target lesions taking as a reference smallest sum of LD recorded since the start of treatment or unequivocal progression in non-target lesions or appearance of 1 or more new lesions. Occurrence of pleural effusion or ascites if demonstrated by cytological investigation, not previously documented. New bone lesions not previously documented if confirmed by computed tomography/magnetic resonance imaging or X-ray. FAS.

End point type	Secondary

End point timeframe:

From initiation of treatment up to follow-up period (up to 3 years)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	362		
Units: Percentage of Subjects				
number (confidence interval 95%)	19.4 (15.4 to 23.9)	9.4 (6.6 to 12.9)		

Statistical analyses

Statistical analysis title	Axitinib vs Sorafenib
Comparison groups	Axitinib 5 mg v Sorafenib 400 mg
Number of subjects included in analysis	723
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	2.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.408
upper limit	3.003

Notes:

[3] - P-value was obtained from a 1-sided Cochran-Mantel-Haenszel test of treatment stratified by ECOG performance status and prior treatment.

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

DR: time from first documentation of objective tumor response (CR or PR), that was subsequently confirmed, to first documentation of PD or to death due to any cause, whichever occurred first as per RECIST version 1.0, a) CR: disappearance of all target, non target lesions and no appearance of new lesions, documented on 2 occasions separated by at least 4 weeks, b) PR: at least 30 % decrease in sum of LD of target lesions taking as reference baseline sum of LD, without progression of non target lesions, no appearance of new lesions, c) PD: >=20% increase in sum of LD of the target lesions taking as a reference smallest sum of LD recorded since the start of treatment or unequivocal progression in non-target lesions or appearance of 1 or more new lesions. Occurrence of pleural effusion or ascites if demonstrated by cytological investigation, not previously documented. New bone lesions not previously documented if confirmed by computed tomography/magnetic resonance imaging or X-ray. FAS.

End point type	Secondary

End point timeframe:

From initiation of treatment up to follow-up period (up to 3 years)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361[4]	362		
Units: Months				
median (confidence interval 95%)	11 (7.4 to 99999)	10.6 (8.8 to 11.5)		

Notes:

[4] - 99999: upper limit of 95% confidence interval was not reached at time of data cut-off.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. A treatment emergent AE was defined as an event that emerged during the treatment period that was absent before treatment, or worsened during the treatment period relative to the pretreatment state. AEs included both serious and nonserious AEs. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

From initiation of treatment up to follow-up period (up to 3 years)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	355		
Units: Percentage of Subjects				
number (not applicable)				
AEs	96.1	98		
SAEs	40.7	35.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs) by Severity

End point title	Percentage of Subjects With Adverse Events (AEs) by Severity

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Severity of the AEs was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Grade 1= mild; Grade 2= moderate; Grade 3= severe; Grade 4= life-threatening or disabling; Grade 5= death related to AE. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

From initiation of treatment up to follow-up period (up to 3 years)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	355		
Units: Percentage of Subjects				
number (not applicable)				
Grade 1	3.9	3.1		
Grade 2	20.1	21.7		
Grade 3	47.6	52.4		
Grade 4	10.6	11.5		
Grade 5	13.9	9.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Treatment-Related Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. AEs included both serious and non serious AEs. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received.

End point type	Secondary

End point timeframe:

From initiation of treatment up to follow-up period (up to 3 years)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	355		
Units: Percentage of Subjects				
number (not applicable)				
AEs	92.2	95.2		
SAEs	15.3	13.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Laboratory Abnormalities: Hematology

End point title	Number of Subjects With Clinically Significant Laboratory Abnormalities: Hematology

End point description:

Hematology laboratory test included hemoglobin, platelet count, white blood cells count, neutrophils and Lymphocytes. Abnormalities were assessed by CTCAE Grade Version 2 for severity: Grade 1= mild; Grade 2= moderate; Grade 3= severe and Grade 4= life-threatening or disabling. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. Here, "n" signifies number of subjects available for specified categories for each arm respectively.

End point type	Secondary

End point timeframe:

From initiation of treatment up to follow-up period (up to 3 years)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	355		
Units: Subjects				
number (not applicable)				
Hemoglobin: Grade 1 (n =320, 316)	93	112		
Hemoglobin: Grade 2 (n =320, 316)	19	41		

Hemoglobin: Grade 3 (n =320, 316)	1	11		
Hemoglobin: Grade 4 (n =320, 316)	0	1		
Lymphocytes: Grade 1 (n =317, 309)	7	7		
Lymphocytes: Grade 2 (n =317, 309)	89	93		
Lymphocytes: Grade 3 (n =317, 309)	10	11		
Lymphocytes: Grade 4 (n =317, 309)	0	0		
Neutrophils: Grade 1 (n =316, 308)	13	20		
Neutrophils: Grade 2 (n =316, 308)	4	4		
Neutrophils: Grade 3 (n =316, 308)	2	2		
Neutrophils: Grade 4 (n =316, 308)	0	0		
Platelets: Grade 1 (n =312, 310)	47	41		
Platelets: Grade 2 (n =312, 310)	0	3		
Platelets: Grade 3 (n =312, 310)	1	0		
Platelets: Grade 4 (n =312, 310)	0	0		
White blood cells: Grade 1 (n =320, 315)	32	36		
White blood cells: Grade 2 (n =320, 315)	4	12		
White blood cells: Grade 3 (n =320, 315)	0	1		
White blood cells: Grade 4 (n =320, 315)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Laboratory Abnormalities: Biochemistry

End point title	Number of Subjects With Clinically Significant Laboratory Abnormalities: Biochemistry

End point description:

Biochemistry laboratory test included parameters: alanine aminotransferase, alkaline phosphatase, amylase, aspartate aminotransferase, bicarbonate, bilirubin, creatinine, hypercalcemia, hyperglycemia, hyperkalemia, hypernatremia, hypoalbuminemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia and lipase. Abnormalities were assessed by CTCAE Grade Version 2 for severity: Grade 1= mild; Grade 2= moderate; Grade 3= severe and Grade 4= life-threatening or disabling. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. Here, "n" signifies number of subjects available for specified categories for each arm respectively.

End point type	Secondary

End point timeframe:

From initiation of treatment up to follow-up period (up to 3 years)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	355		
Units: Subjects				
number (not applicable)				
Alanine aminotransferase: Grade 1 (n =331, 313)	65	57		
Alanine aminotransferase: Grade 2 (n =331, 313)	8	6		
Alanine aminotransferase: Grade 3 (n =331, 313)	1	2		
Alanine aminotransferase: Grade 4 (n =331, 313)	0	3		
Alkaline phosphatase: Grade 1 (n =336, 319)	88	92		
Alkaline phosphatase: Grade 2 (n =336, 319)	8	15		
Alkaline phosphatase: Grade 3 (n =336, 319)	4	3		
Alkaline phosphatase: Grade 4 (n =336, 319)	0	0		
Amylase: Grade 1 (n =338, 319)	64	76		
Amylase: Grade 2 (n =338, 319)	12	21		
Amylase: Grade 3 (n =338, 319)	7	6		
Amylase: Grade 4 (n =338, 319)	0	1		
Aspartate aminotransferase: Grade 1 (n =331, 311)	59	67		
Aspartate aminotransferase: Grade 2 (n =331, 311)	5	7		
Aspartate aminotransferase: Grade 3 (n =331, 311)	1	4		
Aspartate aminotransferase: Grade 4 (n =331, 311)	0	0		
Bicarbonate: Grade 1 (n =314, 291)	127	115		
Bicarbonate: Grade 2 (n =314, 291)	11	10		
Bicarbonate: Grade 3 (n =314, 291)	0	0		
Bicarbonate: Grade 4 (n =314, 291)	1	0		
Bilirubin: Grade 1 (n =336, 318)	16	12		
Bilirubin: Grade 2 (n =336, 318)	8	2		
Bilirubin: Grade 3 (n =336, 318)	1	1		
Bilirubin: Grade 4 (n =336, 318)	0	0		
Creatinine: Grade 1 (n =336, 318)	155	121		
Creatinine: Grade 2 (n =336, 318)	30	9		
Creatinine: Grade 3 (n =336, 318)	0	1		
Creatinine: Grade 4 (n =336, 318)	0	0		
Hypercalcemia: Grade 1 (n =336, 319)	92	22		
Hypercalcemia: Grade 2 (n =336, 319)	8	1		
Hypercalcemia: Grade 3 (n =336, 319)	1	0		
Hypercalcemia: Grade 4 (n =336, 319)	0	0		
Hyperglycemia: Grade 1 (n =336, 319)	41	28		
Hyperglycemia: Grade 2 (n =336, 319)	45	37		
Hyperglycemia: Grade 3 (n =336, 319)	7	7		
Hyperglycemia: Grade 4 (n =336, 319)	0	0		
Hyperkalemia: Grade 1 (n =333, 314)	0	0		
Hyperkalemia: Grade 2 (n =333, 314)	42	22		

Hyperkalemia: Grade 3 (n =333, 314)	9	8		
Hyperkalemia: Grade 4 (n =333, 314)	0	0		
Hypernatremia: Grade 1 (n =338, 319)	34	23		
Hypernatremia: Grade 2 (n =338, 319)	19	14		
Hypernatremia: Grade 3 (n =338, 319)	3	1		
Hypernatremia: Grade 4 (n =338, 319)	0	2		
Hypoalbuminemia: Grade 1 (n =337, 319)	37	25		
Hypoalbuminemia: Grade 2 (n =337, 319)	11	31		
Hypoalbuminemia: Grade 3 (n =337, 319)	1	2		
Hypoalbuminemia: Grade 4 (n =337, 319)	0	0		
Hypocalcemia: Grade 1 (n =336, 319)	25	67		
Hypocalcemia: Grade 2 (n =336, 319)	4	18		
Hypocalcemia: Grade 3 (n =336, 319)	2	2		
Hypocalcemia: Grade 4 (n =336, 319)	1	2		
Hypoglycemia: Grade 1 (n =336, 319)	23	9		
Hypoglycemia: Grade 2 (n =336, 319)	12	16		
Hypoglycemia: Grade 3 (n =336, 319)	1	1		
Hypoglycemia: Grade 4 (n =336, 319)	0	0		
Hypokalemia: Grade 1 (n =333, 314)	22	21		
Hypokalemia: Grade 2 (n =333, 314)	0	0		
Hypokalemia: Grade 3 (n =333, 314)	0	5		
Hypokalemia: Grade 4 (n =333, 314)	0	0		
Hyponatremia: Grade 1 (n =338, 319)	33	27		
Hyponatremia: Grade 2 (n =338, 319)	0	0		
Hyponatremia: Grade 3 (n =338, 319)	11	6		
Hyponatremia: Grade 4 (n =338, 319)	1	1		
Hypophosphatemia: Grade 1 (n =336, 318)	4	8		
Hypophosphatemia: Grade 2 (n =336, 318)	33	99		
Hypophosphatemia: Grade 3 (n =336, 318)	6	51		
Hypophosphatemia: Grade 4 (n =336, 318)	0	0		
Lipase: Grade 1 (n =338, 319)	53	76		
Lipase: Grade 2 (n =338, 319)	22	25		
Lipase: Grade 3 (n =338, 319)	14	40		
Lipase: Grade 4 (n =338, 319)	2	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Laboratory Abnormalities: Urinalysis

End point title	Number of Subjects With Clinically Significant Laboratory Abnormalities: Urinalysis

End point description:

Urinalysis included urine blood/ hemoglobin, glucose and protein. Abnormalities were assessed by CTCAE Grade Version 2 for severity: Grade 1= mild; Grade 2= moderate; Grade 3= severe and Grade 4= life-threatening or disabling. Safety population included all subjects who received at least 1 dose of study medication with treatment assignments designated according to actual study treatment received. Here, "n" signifies number of subjects available for specified categories for each arm respectively.

End point type	Secondary

End point timeframe:

From initiation of treatment up to follow-up period (up to 3 years)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	359	355		
Units: Subjects				
number (not applicable)				
Urine blood/ hemoglobin: Grade 1 (n =304, 272)	45	35		
Urine blood/ hemoglobin: Grade 2 (n =304, 272)	1	0		
Urine blood/ hemoglobin: Grade 3 (n =304, 272)	0	0		
Urine blood/ hemoglobin: Grade 4 (n =304, 272)	0	0		
Urine glucose: Grade 1 (n =322, 286)	12	13		
Urine glucose: Grade 2 (n =322, 286)	0	3		
Urine glucose: Grade 3 (n =322, 286)	0	0		
Urine glucose: Grade 4 (n =322, 286)	1	1		
Urine protein: Grade 1 (n =326, 289)	105	91		
Urine protein: Grade 2 (n =326, 289)	31	27		
Urine protein: Grade 3 (n =326, 289)	27	21		
Urine protein: Grade 4 (n =326, 289)	9	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy Kidney Symptom Index-15 (FKSI-15) Score

End point title	Functional Assessment of Cancer Therapy Kidney Symptom Index-15 (FKSI-15) Score

End point description:

FKSI was used to assess quality of life (QoL) for those diagnosed with renal cell cancer and consisted of 15 items (lack of energy, side effects, pain, losing weight, bone pain, fatigue, enjoying life, short of breath, worsened condition, appetite, coughing, bothered by fevers, ability to work, hematuria and sleep). Each of the 15 items was answered on a 5-point Likert-type scale ranging from 0 to 4 (0= not at all, 1= a little bit, 2= somewhat, 3= quite a bit, 4= very much). Total FKSI score = sum of the 15 item scores; total range: 0 - 60; 0 (no symptoms) to 60 (very much); higher scores indicate greater presence of symptoms. FAS. Here, "n" signifies those subjects who were evaluable for the specified time points.

End point type	Secondary

End point timeframe:

Baseline (Predose on Cycle 1 Day 1) , Day 1 of each cycle until Cycle 21, End of treatment (Day 670) and Follow-up visit (Day 698)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	362		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =346, 342)	43.199 (± 8.416)	43.339 (± 8.162)		
Cycle 2/Day1 (n =319, 296)	42.351 (± 8.305)	41.688 (± 7.696)		
Cycle 3/Day1 (n =279, 246)	42.59 (± 7.729)	42.424 (± 7.888)		
Cycle 4/Day1 (n =257, 221)	42.791 (± 8.18)	43.424 (± 7.345)		
Cycle 5/Day1 (n =238, 203)	42.968 (± 8.152)	42.907 (± 7.255)		
Cycle 6/Day1 (n =213, 179)	42.949 (± 7.842)	43.057 (± 7.724)		
Cycle 7/Day1 (n =206, 158)	42.747 (± 7.621)	43.578 (± 7.621)		
Cycle 8/Day1 (n =177, 136)	43.58 (± 7.578)	44.074 (± 7.757)		
Cycle 9/Day1 (n =163, 118)	43.191 (± 8.3)	44.518 (± 6.511)		
Cycle 10/Day1 (n =146, 96)	43.312 (± 8.564)	44.771 (± 7.155)		
Cycle 11/Day1 (n =122, 85)	44.119 (± 8.306)	44.438 (± 7.388)		
Cycle 12/Day1 (n =110, 70)	44.517 (± 8.212)	44.357 (± 7.247)		
Cycle 13/Day1 (n =92, 58)	44.492 (± 7.972)	45.261 (± 7.84)		
Cycle 14/Day1 (n =81, 54)	44.485 (± 8.204)	44.898 (± 7.495)		
Cycle 15/Day1 (n =61, 38)	45.291 (± 7.095)	45.053 (± 6.682)		
Cycle 16/Day1 (n =52, 34)	45.217 (± 7.656)	44.445 (± 7.16)		
Cycle 17/Day1 (n =47, 28)	45.242 (± 7.344)	44.438 (± 7.683)		
Cycle 18/Day1 (n =36, 22)	44.861 (± 7.769)	44.182 (± 7.228)		
Cycle 19/Day1 (n =29, 14)	45.379 (± 6.662)	45.026 (± 7.705)		
Cycle 20/Day1 (n =20, 12)	47.05 (± 5.375)	44.78 (± 6.689)		
Cycle 21/Day1 (n =15, 7)	45.85 (± 5.209)	44.494 (± 6.153)		
End of treatment (n=163, 191)	38.328 (± 9.472)	38.457 (± 8.787)		
Follow up (n =80, 110)	41.919 (± 8.318)	40.028 (± 9.048)		

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) Score

End point title	Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) Score

End point description:

FKSI-DRS was used to assess quality of life for those diagnosed with renal cell cancer and consisted of 9 items (lack of energy, pain, losing weight, bone pain, fatigue, short of breath, coughing, bothered by fevers, and hematuria). Each of the 9 items was answered on a 5-point Likert-type scale ranging from 0 to 4 (0= not at all, 1= a little bit, 2= somewhat, 3= quite a bit, 4= very much). Total FKSI-DRS score = sum of the 9 item scores; total range: 0 - 36; 0 (no symptoms) to 36 (very much); higher scores indicate greater presence of symptoms. FAS. Here, "n" signifies those subjects who were evaluable for the specified time points.

End point type	Secondary

End point timeframe:

Baseline (Predose on Cycle 1 Day 1) , Day 1 of each cycle until Cycle 21, End of treatment (Day 670) and Follow-up visit (Day 698)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	362		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =346, 341)	28.874 (± 5.187)	28.975 (± 5.193)		
Cycle 2/Day1 (n =319, 295)	28.211 (± 4.92)	28.399 (± 5.064)		
Cycle 3/Day1 (n =279, 244)	28.64 (± 4.837)	28.64 (± 4.868)		
Cycle 4/Day1 (n =257, 220)	28.822 (± 4.952)	29.13 (± 4.322)		
Cycle 5/Day1 (n =238, 202)	28.869 (± 4.88)	29.007 (± 4.379)		
Cycle 6/Day1 (n =213, 178)	29.159 (± 4.462)	29.098 (± 4.697)		
Cycle 7/Day1 (n =206, 157)	29.042 (± 4.581)	29.361 (± 4.558)		
Cycle 8/Day1 (n =177, 135)	29.52 (± 4.346)	29.619 (± 4.386)		
Cycle 9/Day1 (n =163, 117)	29.194 (± 4.937)	29.884 (± 3.838)		
Cycle 10/Day1 (n =146, 96)	29.343 (± 4.907)	29.604 (± 3.959)		
Cycle 11/Day1 (n =122, 85)	29.762 (± 4.943)	29.366 (± 4.404)		

Cycle 12/Day1 (n =110, 70)	29.764 (± 4.507)	29.257 (± 4.299)		
Cycle 13/Day1 (n =92, 58)	29.594 (± 4.205)	29.666 (± 4.71)		
Cycle 14/Day1 (n =81, 54)	29.711 (± 4.313)	29.82 (± 4.333)		
Cycle 15/Day1 (n =61, 38)	30.324 (± 3.582)	29.5 (± 3.454)		
Cycle 16/Day1 (n =52, 34)	30.43 (± 3.443)	29.474 (± 4.146)		
Cycle 17/Day1 (n =47, 28)	30.551 (± 3.331)	28.737 (± 4.93)		
Cycle 18/Day1 (n =36, 22)	30.194 (± 3.992)	29.045 (± 4.52)		
Cycle 19/Day1 (n =29, 14)	30.13 (± 3.636)	29.286 (± 4.795)		
Cycle 20/Day1 (n =20, 12)	31.3 (± 2.736)	29.25 (± 4.025)		
Cycle 21/Day1 (n =15, 7)	31.067 (± 3.173)	30.143 (± 4.1)		
End of Treatment (n =163, 191)	26.288 (± 5.806)	26.517 (± 5.614)		
Follow up (n =80, 110)	28.263 (± 4.802)	27.516 (± 5.577)		

Statistical analyses

No statistical analyses for this end point

Secondary: Euro Quality of Life Questionnaire-5 Dimension (EQ-5D): Health State Profile Utility Score

End point title	Euro Quality of Life Questionnaire-5 Dimension (EQ-5D): Health State Profile Utility Score

End point description:

EQ-5D: subject rated questionnaire to assess health-related quality of life in terms of a single utility or index score. Health state profile component assesses level of health for 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain was rated on a 3-point response scale (1= no problems, 2= some/moderate problems and 3= extreme problems). Scoring formula developed by EuroQol Group assigned a utility value for each domain in the profile. Score were transformed and resulted in a total score range of 0 to 1, with higher scores indicating better health. FAS. Here, "n" signifies those subjects who were evaluable for the specified time points.

End point type	Secondary

End point timeframe:

Baseline (Predose on Cycle 1 Day 1) , Day 1 of each cycle until Cycle 21, End of treatment (Day 670) and Follow-up visit (Day 698)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	362		
Units: Units on a scale				
arithmetic mean (standard deviation)				

Baseline (n =347, 341)	0.732 (± 0.275)	0.731 (± 0.257)		
Cycle 2/Day1 (n =326, 307)	0.716 (± 0.267)	0.696 (± 0.237)		
Cycle 3/Day1 (n =287, 248)	0.722 (± 0.243)	0.709 (± 0.239)		
Cycle 4/Day1 (n =262, 226)	0.73 (± 0.236)	0.716 (± 0.248)		
Cycle 5/Day1 (n =244, 207)	0.73 (± 0.237)	0.711 (± 0.243)		
Cycle 6/Day1 (n =221, 178)	0.734 (± 0.23)	0.704 (± 0.246)		
Cycle 7/Day1 (n =213, 163)	0.718 (± 0.267)	0.728 (± 0.228)		
Cycle 8/Day1 (n =181, 136)	0.756 (± 0.236)	0.702 (± 0.259)		
Cycle 9/Day1 (n =169, 120)	0.76 (± 0.227)	0.73 (± 0.229)		
Cycle 10/Day1 (n =151, 98)	0.734 (± 0.243)	0.73 (± 0.233)		
Cycle 11/Day1 (n =126, 87)	0.764 (± 0.235)	0.724 (± 0.25)		
Cycle 12/Day1 (n =110, 73)	0.744 (± 0.244)	0.734 (± 0.232)		
Cycle 13/Day1 (n =96, 61)	0.76 (± 0.211)	0.753 (± 0.232)		
Cycle 14/Day1 (n =80, 57)	0.723 (± 0.239)	0.752 (± 0.211)		
Cycle 15/Day1 (n =63, 41)	0.73 (± 0.255)	0.758 (± 0.191)		
Cycle 16/Day1 (n =54, 37)	0.749 (± 0.22)	0.785 (± 0.158)		
Cycle 17/Day1 (n =48, 29)	0.779 (± 0.186)	0.764 (± 0.193)		
Cycle 18/Day1 (n =37, 20)	0.755 (± 0.204)	0.755 (± 0.208)		
Cycle 19/Day1 (n =29, 14)	0.734 (± 0.253)	0.804 (± 0.184)		
Cycle 20/Day1 (n =21, 12)	0.794 (± 0.22)	0.771 (± 0.182)		
Cycle 21/Day1 (n =16, 7)	0.7 (± 0.273)	0.771 (± 0.186)		
End of Treatment (n =169, 196)	0.608 (± 0.316)	0.612 (± 0.31)		
Follow up (n =76, 106)	0.682 (± 0.294)	0.666 (± 0.295)		

Statistical analyses

No statistical analyses for this end point

Secondary: Euro Quality of Life Questionnaire-5 Dimension (EQ-5D): Visual Analog Scale (VAS)

End point title	Euro Quality of Life Questionnaire-5 Dimension (EQ-5D): Visual Analog Scale (VAS)

End point description:

EQ-5D: subject rated questionnaire to assess health-related quality of life in terms of a single index value. VAS component: subjects rated their current health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state); higher scores indicate a better health. FAS. Here,

"n" signifies those subjects who were evaluable for the specified time points.

End point type	Secondary

End point timeframe:

Baseline (Predose on Cycle 1 Day 1) , Day 1 of each cycle until Cycle 21, End of treatment (Day 670) and Follow-up visit (Day 698)

End point values	Axitinib 5 mg	Sorafenib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	362		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =341, 339)	70.56 (± 19.187)	70.351 (± 17.403)		
Cycle 2/Day1 (n =317, 302)	69.003 (± 20.195)	67.606 (± 18.265)		
Cycle 3/Day1 (n =280, 250)	69.843 (± 17.927)	69.712 (± 18.429)		
Cycle 4/Day1 (n =261, 224)	69.18 (± 18.636)	70.759 (± 17.189)		
Cycle 5/Day1 (n =244, 205)	69.705 (± 18.33)	71.888 (± 16.999)		
Cycle 6/Day1 (n =220, 178)	69.9 (± 18.168)	71.365 (± 17.019)		
Cycle 7/Day1 (n =209, 163)	69.919 (± 18.063)	72.282 (± 17.521)		
Cycle 8/Day1 (n =180, 139)	70.756 (± 19.183)	71.475 (± 18.523)		
Cycle 9/Day1 (n =168, 121)	70.667 (± 18.556)	73.38 (± 17.473)		
Cycle 10/Day1 (n =151, 98)	70.629 (± 18.68)	75.102 (± 14.854)		
Cycle 11/Day1 (n =126, 87)	72.103 (± 18.064)	74.586 (± 15.161)		
Cycle 12/Day1 (n =111, 73)	71.73 (± 17.276)	73.959 (± 15.852)		
Cycle 13/Day1 (n =94, 61)	70.723 (± 19.147)	75.693 (± 14.571)		
Cycle 14/Day1 (n =81, 58)	69.42 (± 20.286)	75.362 (± 15.875)		
Cycle 15/Day1 (n =62, 42)	73.016 (± 15.325)	75.357 (± 15.368)		
Cycle 16/Day1 (n =52, 37)	70.629 (± 19.272)	73.676 (± 15.699)		
Cycle 17/Day1 (n =48, 30)	71.357 (± 17.84)	73.676 (± 16.298)		
Cycle 18/Day1 (n =37, 23)	70.459 (± 18.853)	73.87 (± 16.904)		
Cycle 19/Day1 (n =29, 14)	71.034 (± 16.963)	70.571 (± 17.956)		
Cycle 20/Day1 (n =21, 12)	73.143 (± 15.347)	66.917 (± 17.758)		
Cycle 21/Day1 (n =16, 7)	74.563 (± 16.054)	64.714 (± 16.183)		
End of Treatment (n =166, 197)	61.759 (± 21.668)	61.69 (± 20.973)		

Follow up (n =76, 109)	64.382 (± 21.392)	66.037 (± 19.754)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From initiation of treatment up to follow-up period (up to 3 years)

Adverse event reporting additional description:

Same event may appear as both AE and SAE, what is presented are distinct event. Event may be classified as serious in 1 subject, nonserious in other, or 1 subject may have experienced both serious, nonserious event during study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Axitinib 5 mg

Reporting group description:

Axitinib (AG-013736) 5 mg tablet administered orally twice daily in cycles of 4 weeks.

Reporting group title	Sorafenib 400 mg

Reporting group description:

Sorafenib 400 mg tablet administered orally twice daily in cycles of 4 weeks.

Serious adverse events	Axitinib 5 mg	Sorafenib 400 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	146 / 359 (40.67%)	127 / 355 (35.77%)	
number of deaths (all causes)	55	42	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastasis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			

subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 359 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 359 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 359 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 359 (0.28%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pain management			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebroplasty			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 359 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chest pain			
subjects affected / exposed	2 / 359 (0.56%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chills			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 359 (0.84%)	6 / 355 (1.69%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	3 / 3	4 / 6	
Device dislocation			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	32 / 359 (8.91%)	18 / 355 (5.07%)	
occurrences causally related to treatment / all	0 / 33	0 / 19	
deaths causally related to treatment / all	0 / 29	0 / 18	
Fatigue			
subjects affected / exposed	4 / 359 (1.11%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	3 / 359 (0.84%)	5 / 355 (1.41%)	
occurrences causally related to treatment / all	1 / 3	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Hernia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			

subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 359 (0.56%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 359 (1.95%)	5 / 355 (1.41%)	
occurrences causally related to treatment / all	3 / 8	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia	Additional description: This event was gender specific.		
subjects affected / exposed[1]	1 / 265 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Menometrorrhagia	Additional description: This event was gender specific.		
subjects affected / exposed[2]	0 / 96 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal polyp	Additional description: This event was gender specific.		
subjects affected / exposed[3]	1 / 96 (1.04%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	7 / 359 (1.95%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dyspnoea exertional			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 359 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 359 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemothorax			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 359 (0.84%)	5 / 355 (1.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	4 / 359 (1.11%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 359 (1.95%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	2 / 7	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			

subjects affected / exposed	0 / 359 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 359 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 359 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count abnormal			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	1 / 359 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	2 / 359 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 359 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 359 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 359 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			

subjects affected / exposed	2 / 359 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 359 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	2 / 359 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			

subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhage coronary artery			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	6 / 359 (1.67%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	4 / 7	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			

subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 359 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dizziness			
subjects affected / exposed	3 / 359 (0.84%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			

subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	2 / 359 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningeal disorder			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoplegia			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			

subjects affected / exposed	2 / 359 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 359 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	3 / 359 (0.84%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 359 (0.00%)	8 / 355 (2.25%)	
occurrences causally related to treatment / all	0 / 0	4 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery embolism			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			

subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 359 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 359 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 359 (2.23%)	5 / 355 (1.41%)	
occurrences causally related to treatment / all	6 / 8	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			

subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enterocolitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	2 / 359 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 359 (0.00%)	5 / 355 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal perforation			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	3 / 359 (0.84%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	4 / 359 (1.11%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 359 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 359 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Small intestinal obstruction			

subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 359 (1.39%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Budd-Chiari syndrome			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 359 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 359 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 359 (0.00%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperhidrosis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pustular psoriasis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 359 (0.00%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	4 / 359 (1.11%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute prerenal failure			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oliguria			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			

subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary hypothyroidism			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 359 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 359 (0.84%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 359 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			

subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 359 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial diarrhoea			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 359 (0.84%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 359 (0.00%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			

subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle abscess			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 359 (1.39%)	4 / 355 (1.13%)	
occurrences causally related to treatment / all	2 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 359 (0.28%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 359 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Septic shock			
subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 359 (0.56%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 359 (0.84%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	10 / 359 (2.79%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	8 / 10	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 359 (0.28%)	2 / 355 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 359 (0.56%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			

subjects affected / exposed	0 / 359 (0.00%)	1 / 355 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 359 (0.56%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 359 (0.28%)	3 / 355 (0.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 355 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event was gender specific.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event was gender specific.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event was gender specific.

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

Non-serious adverse events	Axitinib 5 mg	Sorafenib 400 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	336 / 359 (93.59%)	334 / 355 (94.08%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	156 / 359 (43.45%)	107 / 355 (30.14%)	
occurrences (all)	318	174	
Hypotension			

subjects affected / exposed	19 / 359 (5.29%)	6 / 355 (1.69%)	
occurrences (all)	20	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	78 / 359 (21.73%)	57 / 355 (16.06%)	
occurrences (all)	203	120	
Chest pain			
subjects affected / exposed	23 / 359 (6.41%)	20 / 355 (5.63%)	
occurrences (all)	34	24	
Fatigue			
subjects affected / exposed	151 / 359 (42.06%)	122 / 355 (34.37%)	
occurrences (all)	366	210	
Mucosal inflammation			
subjects affected / exposed	61 / 359 (16.99%)	45 / 355 (12.68%)	
occurrences (all)	99	83	
Oedema peripheral			
subjects affected / exposed	22 / 359 (6.13%)	22 / 355 (6.20%)	
occurrences (all)	25	35	
Pain			
subjects affected / exposed	19 / 359 (5.29%)	17 / 355 (4.79%)	
occurrences (all)	23	19	
Pyrexia			
subjects affected / exposed	26 / 359 (7.24%)	40 / 355 (11.27%)	
occurrences (all)	31	59	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	68 / 359 (18.94%)	70 / 355 (19.72%)	
occurrences (all)	107	90	
Dysphonia			
subjects affected / exposed	116 / 359 (32.31%)	49 / 355 (13.80%)	
occurrences (all)	158	51	
Dyspnoea			
subjects affected / exposed	64 / 359 (17.83%)	53 / 355 (14.93%)	
occurrences (all)	100	78	
Dyspnoea exertional			

subjects affected / exposed	18 / 359 (5.01%)	11 / 355 (3.10%)	
occurrences (all)	21	13	
Epistaxis			
subjects affected / exposed	28 / 359 (7.80%)	19 / 355 (5.35%)	
occurrences (all)	37	20	
Haemoptysis			
subjects affected / exposed	8 / 359 (2.23%)	18 / 355 (5.07%)	
occurrences (all)	10	21	
Oropharyngeal pain			
subjects affected / exposed	22 / 359 (6.13%)	21 / 355 (5.92%)	
occurrences (all)	37	28	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	33 / 359 (9.19%)	21 / 355 (5.92%)	
occurrences (all)	41	24	
Investigations			
Blood thyroid stimulating hormone increased			
subjects affected / exposed	19 / 359 (5.29%)	11 / 355 (3.10%)	
occurrences (all)	22	16	
Lipase increased			
subjects affected / exposed	13 / 359 (3.62%)	22 / 355 (6.20%)	
occurrences (all)	15	50	
Weight decreased			
subjects affected / exposed	111 / 359 (30.92%)	83 / 355 (23.38%)	
occurrences (all)	216	168	
Nervous system disorders			
Dizziness			
subjects affected / exposed	33 / 359 (9.19%)	21 / 355 (5.92%)	
occurrences (all)	42	28	
Dysgeusia			
subjects affected / exposed	43 / 359 (11.98%)	31 / 355 (8.73%)	
occurrences (all)	56	32	
Headache			
subjects affected / exposed	55 / 359 (15.32%)	43 / 355 (12.11%)	
occurrences (all)	78	59	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	18 / 359 (5.01%)	44 / 355 (12.39%)	
occurrences (all)	28	106	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	55 / 359 (15.32%)	46 / 355 (12.96%)	
occurrences (all)	95	69	
Abdominal pain upper			
subjects affected / exposed	37 / 359 (10.31%)	16 / 355 (4.51%)	
occurrences (all)	50	20	
Constipation			
subjects affected / exposed	79 / 359 (22.01%)	82 / 355 (23.10%)	
occurrences (all)	116	101	
Diarrhoea			
subjects affected / exposed	208 / 359 (57.94%)	195 / 355 (54.93%)	
occurrences (all)	736	449	
Dyspepsia			
subjects affected / exposed	39 / 359 (10.86%)	15 / 355 (4.23%)	
occurrences (all)	46	22	
Flatulence			
subjects affected / exposed	20 / 359 (5.57%)	8 / 355 (2.25%)	
occurrences (all)	22	10	
Nausea			
subjects affected / exposed	128 / 359 (35.65%)	84 / 355 (23.66%)	
occurrences (all)	212	138	
Stomatitis			
subjects affected / exposed	60 / 359 (16.71%)	47 / 355 (13.24%)	
occurrences (all)	113	87	
Vomiting			
subjects affected / exposed	95 / 359 (26.46%)	69 / 355 (19.44%)	
occurrences (all)	161	100	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	18 / 359 (5.01%)	122 / 355 (34.37%)	
occurrences (all)	20	145	
Dry skin			

subjects affected / exposed	36 / 359 (10.03%)	42 / 355 (11.83%)	
occurrences (all)	47	47	
Erythema			
subjects affected / exposed	12 / 359 (3.34%)	39 / 355 (10.99%)	
occurrences (all)	14	52	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	100 / 359 (27.86%)	183 / 355 (51.55%)	
occurrences (all)	339	484	
Pruritus			
subjects affected / exposed	25 / 359 (6.96%)	48 / 355 (13.52%)	
occurrences (all)	30	59	
Rash			
subjects affected / exposed	53 / 359 (14.76%)	109 / 355 (30.70%)	
occurrences (all)	72	168	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	49 / 359 (13.65%)	32 / 355 (9.01%)	
occurrences (all)	219	72	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	74 / 359 (20.61%)	33 / 355 (9.30%)	
occurrences (all)	89	36	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	62 / 359 (17.27%)	46 / 355 (12.96%)	
occurrences (all)	111	55	
Back pain			
subjects affected / exposed	59 / 359 (16.43%)	54 / 355 (15.21%)	
occurrences (all)	96	65	
Muscle spasms			
subjects affected / exposed	11 / 359 (3.06%)	21 / 355 (5.92%)	
occurrences (all)	14	30	
Musculoskeletal pain			
subjects affected / exposed	28 / 359 (7.80%)	27 / 355 (7.61%)	
occurrences (all)	41	31	
Myalgia			

subjects affected / exposed	28 / 359 (7.80%)	12 / 355 (3.38%)	
occurrences (all)	43	15	
Pain in extremity			
subjects affected / exposed	49 / 359 (13.65%)	53 / 355 (14.93%)	
occurrences (all)	82	87	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	25 / 359 (6.96%)	13 / 355 (3.66%)	
occurrences (all)	33	13	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	140 / 359 (39.00%)	112 / 355 (31.55%)	
occurrences (all)	279	161	
Dehydration			
subjects affected / exposed	18 / 359 (5.01%)	10 / 355 (2.82%)	
occurrences (all)	26	10	

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