Clinical trial results:
A randomized, double-blind, placebo-controlled, Phase III study to evaluate the efficacy and safety of pazopanib as adjuvant therapy for subjects with localized or locally advanced renal cell carcinoma (RCC) following nephrectomy.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Summary

EudraCT number	2010-020965-26
Trial protocol	SK DE DK IE CZ ES BE GR GB AT PL HU IT
Global end of trial date	15 April 2019

Results information

Result version number	v1
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	113387

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01235962
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	

investigation plan (PIP)	
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	15 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this ongoing study is to evaluate disease free survival (DFS) with pazopanib 600 mg daily initial dose as compared with placebo as adjuvant therapy for subjects with localized/locally advanced RCC following nephrectomy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2010
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	Argentina: 26
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Brazil: 39
Country: Number of subjects enrolled	Canada: 94
Country: Number of subjects enrolled	Chile: 13
Country: Number of subjects enrolled	China: 37
Country: Number of subjects enrolled	Czech Republic: 88
Country: Number of subjects enrolled	Denmark: 55
Country: Number of subjects enrolled	France: 83
Country: Number of subjects enrolled	Germany: 123
Country: Number of subjects enrolled	United Kingdom: 76

Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	Ireland: 34
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Italy: 70
Country: Number of subjects enrolled	Japan: 61
Country: Number of subjects enrolled	Korea, Republic of: 74
Country: Number of subjects enrolled	Luxembourg: 2
Country: Number of subjects enrolled	Poland: 63
Country: Number of subjects enrolled	Russian Federation: 115
Country: Number of subjects enrolled	Slovakia: 42
Country: Number of subjects enrolled	Spain: 53
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United States: 315
Worldwide total number of subjects	1538
EEA total number of subjects	741

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)	1130
From 65 to 84 years	408
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1538 subjects were enrolled and analyzed.

Pre-assignment

Screening details:

The study was planned to include 1500 subjects.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ITT pazopanib 800 mg

Arm description:

Pazopanib 800 mg daily based on safety evaluation. Complete treatment is 12 months.

Arm type	Experimental
Investigational medicinal product name	pazopanib
Investigational medicinal product code	PZP034
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

For subjects randomized prior to the approval of Amendment 2, the scheduled starting dose was 800 mg daily (4 × 200 mg
tablets).

Arm title	ITT placebo 800 mg

Arm description:

Placebo matching pazopanib 800 mg daily. Complete treatment is 12 months.

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

Dosage and administration details:

For subjects randomized prior to the approval of Amendment 2, the scheduled starting dose was 800 mg daily (4 × 200 mg
placebo tablets).

Arm title	ITT pazopanib 600 mg

Arm description:

Pazopanib 600 mg daily initial dose for 8-12 weeks. Dose can be escalated to 800 mg daily based on safety evaluation. Complete treatment is 12 months.

Arm type	Experimental

Investigational medicinal product name	pazopanib
Investigational medicinal product code	PZP034
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subsequent to Amendment 2, each subject started the study treatment at 600 mg daily (3 × 200 mg tablets) for 8 to 12 weeks. Based on evaluation of each subject's safety and tolerability profile, the Investigator determined whether the subject should be dose escalated to 800 mg daily (4 × 200 mg tablets) or maintained at 600 mg daily.

Arm title	ITT placebo 600 mg

Arm description:

Placebo matching pazopanib 600 mg daily. Complete treatment is 12 months.

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

Dosage and administration details:

Subsequent to Amendment 2, each subject started the study treatment at 600 mg daily (3 × 200 mg placebo tablets) for 8 to 12 weeks. Based on evaluation of each subject's safety and tolerability profile, the Investigator determined whether the subject should be dose escalated to 800 mg daily (4 × 200 mg placebo tablets) or maintained at 600 mg daily.

Number of subjects in period 1	ITT pazopanib 800 mg	ITT placebo 800 mg	ITT pazopanib 600 mg
Started	198	205	571
Prem. withdrawn = did not complete study	46 [1]	35 [2]	118 [3]
Completed	152	170	453
Not completed	46	35	118
Consent withdrawn by subject	20	19	62
Physician decision	5	-	9
Lost to follow-up	21	16	47

Number of subjects in period 1	ITT placebo 600 mg
Started	564
Prem. withdrawn = did not complete study	86 [4]
Completed	478
Not completed	86
Consent withdrawn by subject	49
Physician decision	5
Lost to follow-up	32

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This are the subjects who prematurely exited the study and did not complete the study which was fewer that the total number of subjects who continued the study

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This are the subjects who prematurely exited the study and did not complete the study which was fewer that the total number of subjects who continued the study

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This are the subjects who prematurely exited the study and did not complete the study which was fewer that the total number of subjects who continued the study

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This are the subjects who prematurely exited the study and did not complete the study which was fewer that the total number of subjects who continued the study

Baseline characteristics

Reporting groups	
Reporting group title	ITT pazopanib 800 mg
Reporting group description:	
Pazopanib 800 mg daily based on safety evaluation. Complete treatment is 12 months.	
Reporting group title	ITT placebo 800 mg
Reporting group description:	
Placebo matching pazopanib 800 mg daily. Complete treatment is 12 months.	
Reporting group title	ITT pazopanib 600 mg
Reporting group description:	
Pazopanib 600 mg daily initial dose for 8-12 weeks. Dose can be escalated to 800 mg daily based on safety evaluation. Complete treatment is 12 months.	
Reporting group title	ITT placebo 600 mg
Reporting group description:	
Placebo matching pazopanib 600 mg daily. Complete treatment is 12 months.	

Reporting group values	ITT pazopanib 800 mg	ITT placebo 800 mg	ITT pazopanib 600 mg
Number of subjects	198	205	571
Age Categorical Units: Participants			
=>18 to <65	154	140	430
=>65 to <75	36	55	122
=>75 to <85	8	10	19
Sex: Female, Male Units: Participants			
Female	59	51	173
Male	139	154	398
Race/Ethnicity, Customized Units: Subjects			
White	168	178	471
Asian	28	26	71
African American/African Heritage	1	0	7
Other	0	1	4
Missing	1	0	18

Reporting group values	ITT placebo 600 mg	Total	
Number of subjects	564	1538	
Age Categorical Units: Participants			
=>18 to <65	406	1130	
=>65 to <75	131	344	
=>75 to <85	27	64	
Sex: Female, Male Units: Participants			
Female	164	447	
Male	400	1091	

Race/Ethnicity, Customized Units: Subjects			
White	481	1298	
Asian	70	195	
African American/African Heritage	1	9	
Other	2	7	
Missing	10	29	

Subject analysis sets

Subject analysis set title	ITT All - pazopanib
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects with a scheduled initial dose of 600 mg or 800 mg daily pazopanib

Subject analysis set title	ITT All - placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects with a scheduled initial dose of 600 or 800 mg daily placebo

Reporting group values	ITT All - pazopanib	ITT All - placebo	
Number of subjects	769	769	
Age Categorical Units: Participants			
=>18 to <65	584	546	
=>65 to <75	158	186	
=>75 to <85	27	37	
Sex: Female, Male Units: Participants			
Female	232	215	
Male	537	554	
Race/Ethnicity, Customized Units: Subjects			
White	639	659	
Asian	99	96	
African American/African Heritage	8	1	
Other	4	3	
Missing	19	10	

End points

End points reporting groups

Reporting group title	ITT pazopanib 800 mg
Reporting group description:	
Pazopanib 800 mg daily based on safety evaluation. Complete treatment is 12 months.	
Reporting group title	ITT placebo 800 mg
Reporting group description:	
Placebo matching pazopanib 800 mg daily. Complete treatment is 12 months.	
Reporting group title	ITT pazopanib 600 mg
Reporting group description:	
Pazopanib 600 mg daily initial dose for 8-12 weeks. Dose can be escalated to 800 mg daily based on safety evaluation. Complete treatment is 12 months.	
Reporting group title	ITT placebo 600 mg
Reporting group description:	
Placebo matching pazopanib 600 mg daily. Complete treatment is 12 months.	
Subject analysis set title	ITT All - pazopanib
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects with a scheduled initial dose of 600 mg or 800 mg daily pazopanib	
Subject analysis set title	ITT All - placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects with a scheduled initial dose of 600 or 800 mg daily placebo	

Primary: Disease-free survival (DFS) with pazopanib 600 mg daily initial dose vs. placebo

End point title	Disease-free survival (DFS) with pazopanib 600 mg daily initial dose vs. placebo[1]
End point description:	
DFS is defined as the interval between the date of randomization and the earliest date of disease recurrence/metastasis or death due to any cause.	
End point type	Primary
End point timeframe:	
approximately 5 years	

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 statistics was planned for this endpoint

End point values	ITT pazopanib 600 mg	ITT placebo 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	571	564		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	DFS ITT paz 600mg vs. pbo 600mg
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1649
Method	Stratified Log-Rank
Parameter estimate	Adjusted Hazard Ratio
Point estimate	0.862
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.699
upper limit	1.063

Secondary: Overall survival (OS) with pazopanib 600 mg daily initial dose vs. placebo

End point title	Overall survival (OS) with pazopanib 600 mg daily initial dose vs. placebo[2]

End point description:

Overall survival is defined as the time from randomization until death due to any cause.
For subjects who do not die, time to death will be censored at the last date of known contact.

End point type	Secondary

End point timeframe:

approximately 8.5 years

Notes:

[2] - 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 statistics was planned for this endpoint

End point values	ITT pazopanib 600 mg	ITT placebo 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	571	564		
Units: months				
median (confidence interval 95%)	89.5 (9 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	OS ITT paz 600mg vs. pbo 600mg
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg

Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.988
Method	Stratified Log-Rank
Parameter estimate	Adjusted Hazard Ratio
Point estimate	0.998
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.759
upper limit	1.311

Secondary: DFS rates at yearly time points with pazopanib 600 mg daily initial dose vs. placebo

End point title	DFS rates at yearly time points with pazopanib 600 mg daily initial dose vs. placebo[3]

End point description:

End point type	Secondary

End point timeframe:

yearly for 4 years

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 statistics was planned for this endpoint

End point values	ITT pazopanib 600 mg	ITT placebo 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	571	564		
Units: DFS rate				
median (confidence interval 95%)				
DFS at 1 year (n = 423, 394)	0.85 (0.81 to 0.88)	0.76 (0.72 to 0.79)		
DFS at 2 years (n = 308, 300)	0.72 (0.67 to 0.75)	0.68 (0.64 to 0.72)		
DFS at 3 years (n = 118, 118)	0.65 (0.61 to 0.70)	0.64 (0.59 to 0.68)		
DFS at 4 years (n = 0, 0)	0 (0 to 0)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: DFS with pazopanib vs. placebo

End point title	DFS with pazopanib vs. placebo

End point description:

DFS is defined as the interval between the date of randomization and the earliest date of disease

recurrence/metastasis or death due to any cause.

End point type	Secondary

End point timeframe:

approximately 5 years

End point values	ITT All - pazopanib	ITT All - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	769	769		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	99 (48.1 to 999)		

Statistical analyses

Statistical analysis title	DFS ITT All-paz vs. ITT All-pbo
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0126
Method	Stratified Log-Rank
Parameter estimate	Adjusted Hazard Ratio
Point estimate	0.802
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.675
upper limit	0.954

Secondary: OS with pazopanib vs. placebo

End point title	OS with pazopanib vs. placebo

End point description:

Overall survival is defined as the time from randomization until death due to any cause.
For subjects who do not die, time to death will be censored at the last date of known contact.

End point type	Secondary

End point timeframe:

approximately 8.5 years

End point values	ITT All - pazopanib	ITT All - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	769	769		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	OS ITT All-paz vs. ITT All-pbo
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9959
Method	Stratified Log-Rank
Parameter estimate	Adjusted Hazard Ratio
Point estimate	1.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.796
upper limit	1.257

Secondary: DFS rates at yearly time points with pazopanib vs. placebo

End point title	DFS rates at yearly time points with pazopanib vs. placebo

End point description:

End point type	Secondary

End point timeframe:

yearly for 4 years

End point values	ITT All - pazopanib	ITT All - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	769	769		
Units: DFS rate				
median (confidence interval 95%)				
DFS at 1 year (n = 579, 538)	0.85 (0.82 to 0.87)	0.75 (0.72 to 0.78)		
DFS at 2 years (n = 436, 419)	0.72 (0.68 to 0.75)	0.66 (0.63 to 0.70)		
DFS at 3 years (n = 231, 215)	0.65 (0.62 to 0.69)	0.61 (0.58 to 0.65)		

DFS at 4 years (n = 48, 46)	0.62 (0.58 to 0.66)	0.56 (0.51 to 0.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: DFS pazopanib 800 mg daily initial dose vs. placebo

End point title	DFS pazopanib 800 mg daily initial dose vs. placebo[4]

End point description:

DFS is defined as the interval between the date of randomization and the earliest date of disease recurrence/metastasis or death due to any cause.

End point type	Secondary

End point timeframe:

approximately 5 years

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 statistics was planned for this endpoint

End point values	ITT pazopanib 800 mg	ITT placebo 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	205		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	48.1 (30.1 to 999)		

Statistical analyses

Statistical analysis title	DFS ITT paz 800mg vs. pbo 800mg
Comparison groups	ITT pazopanib 800 mg v ITT placebo 800 mg
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0201
Method	Stratified Log-Rank
Parameter estimate	Adjusted Hazard Ratio
Point estimate	0.693
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.943

Secondary: OS with pazopanib 800 mg daily initial dose vs. placebo

End point title	OS with pazopanib 800 mg daily initial dose vs. placebo[5]

End point description:

Overall survival is defined as the time from randomization until death due to any cause.
For subjects who do not die, time to death will be censored at the last date of known contact.

End point type	Secondary

End point timeframe:

approximately 8.5 years

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 statistics was planned for this endpoint

End point values	ITT pazopanib 800 mg	ITT placebo 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	198	205		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

Statistical analysis title	OS ITT paz 800mg vs. pbo 800mg
Comparison groups	ITT pazopanib 800 mg v ITT placebo 800 mg
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9865
Method	Stratified Log-Rank
Parameter estimate	Adjusted Hazard Ratio
Point estimate	1.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.662
upper limit	1.521

Secondary: Health-related quality of life (HRQoL) with pazopanib 600 mg daily initial dose vs. placebo assessed using NCCN/Functional Assessment of Cancer Therapy-Kidney Symptom Index -19 (FACT FKSI-19) total score

End point title	Health-related quality of life (HRQoL) with pazopanib 600 mg daily initial dose vs. placebo assessed using NCCN/Functional Assessment of Cancer Therapy-Kidney Symptom Index -19 (FACT FKSI-19) total score[6]

End point description:

Health outcome and quality of life as measured by NCCN/FACT FKSI-19 questionnaire. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. The total score assesses for all 4 symptoms (FKSI-DRS-P, FKSI-DRS-E, FKSI-TSE, FKSI-F/WB) experienced in the past 7 days. Participants are asked to respond to 12 questions

("I have a lack of energy," "I feel pain," for example) by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 48). Higher scores represent better health. DFS: disease-free survival; FU: follow up

End point type	Secondary

End point timeframe:

Week 52, 24M DFS FU, 36M DFS FU, 48M DFS FU, 54M DFS FU

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 statistics was planned for this endpoint

End point values	ITT pazopanib 600 mg	ITT placebo 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	571	564		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 (n = 423, 401)	-3.83 (± 0.452)	-0.43 (± 0.459)		
24M DFS FU (n = 335, 340)	0.19 (± 0.419)	0.23 (± 0.418)		
36M DFS FU (n = 294, 290)	-0.14 (± 0.454)	-0.26 (± 0.456)		
48M DFS FU (n = 144, 140)	-0.13 (± 0.526)	0.22 (± 0.529)		
54M DFS FU (n = 60, 66)	0.09 (± 0.653)	0.26 (± 0.635)		

Statistical analyses

Statistical analysis title	FACT FKSI-19 (600 mg) total score - W52
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52)
Point estimate	-3.397
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.486
upper limit	-2.307

Statistical analysis title	FACT FKSI-19 (600 mg) total score - 24M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg

Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	analysis of covariance
Parameter estimate	Mean Difference (24M DFS FU)
Point estimate	-0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.003
upper limit	0.917

Statistical analysis title	FACT FKSI-19 (600 mg) total score - 36M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.828
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU)
Point estimate	0.119
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.958
upper limit	1.196

Statistical analysis title	FACT FKSI-19 (600 mg) total score - 48M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.603
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU)
Point estimate	-0.347
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.658
upper limit	0.964

Statistical analysis title	FACT FKSI-19 (600 mg) total score - 54M DFS FU

Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.841
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU)
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.843
upper limit	1.503

Secondary: Health-related quality of life (HRQoL) with pazopanib 600 mg daily initial dose vs. placebo assessed using NCCN/FACT FKSI-19 Scale Disease-related Symptoms-physical (DRS-P) Domain score

End point title	Health-related quality of life (HRQoL) with pazopanib 600 mg daily initial dose vs. placebo assessed using NCCN/FACT FKSI-19 Scale Disease-related Symptoms-physical (DRS-P) Domain score[7]

End point description:

Health outcome and quality of life as measured by NCCN/FACT FKSI-19 questionnaire. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. The DRS-P domain assesses symptoms experienced in the past 7 days. Participants are asked to respond to 12 questions ("I have a lack of energy," "I feel pain," for example) by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 48). Higher scores represent better health.

End point type	Secondary

End point timeframe:

Week 52, 24M DFS FU, 36M DFS FU, 48M DFS FU, 54M DFS FU

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 statistics was planned for this endpoint

End point values	ITT pazopanib 600 mg	ITT placebo 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	571	564		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 (n = 427, 406)	-2.06 (± 0.278)	-0.44 (± 0.282)		
24M DFS FU (n = 340, 341)	-0.32 (± 0.273)	-0.20 (± 0.273)		
36M DFS FU (n = 300, 293)	-0.61 (± 0.291)	-0.53 (± 0.294)		
48M DFS FU (n = 147, 141)	-0.67 (± 0.332)	-0.46 (± 0.336)		
54M DFS FU (n = 61, 66)	-0.21 (± 0.449)	-0.55 (± 0.439)		

Statistical analyses

Statistical analysis title	FACT FKSI-19 (600 mg) DRS-P score - W52
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52)
Point estimate	-1.619
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.283
upper limit	-0.955

Statistical analysis title	FACT FKSI-19 (600 mg) DRS-P score - 24M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.726
Method	analysis of covariance
Parameter estimate	Mean Difference (24 M DFS FU)
Point estimate	-0.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	0.522

Statistical analysis title	FACT FKSI-19 (600 mg) DRS-P score - 36M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg

Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.801
Method	analysis of covariance
Parameter estimate	Mean Difference (36 M DFS FU)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.789
upper limit	0.609

Statistical analysis title	FACT FKSI-19 (600 mg) DRS-P score - 48M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.617
Method	analysis of covariance
Parameter estimate	Meat Difference (48 M DFS FU)
Point estimate	-0.212
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.044
upper limit	0.32

Statistical analysis title	FACT FKSI-19 (600 mg) DRS-P score - 54M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.565
Method	adjusted for baseline score using mixedm
Parameter estimate	Mean Difference (54 M DFS FU)
Point estimate	0.341
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.828
upper limit	1.51

Secondary: Health-related quality of life (HRQoL) with pazopanib 600 mg daily

initial dose vs. placebo assessed using NCCN/FACT FKSI-19 Scale Disease Related Symptoms-emotional (DRS-E) Domain Score

End point title	Health-related quality of life (HRQoL) with pazopanib 600 mg daily initial dose vs. placebo assessed using NCCN/FACT FKSI-19 Scale Disease Related Symptoms-emotional (DRS-E) Domain Score[8]

End point description:

Health outcome and quality of life as measured by NCCN/FACT FKSI-19 questionnaire. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. The DRS-E domain assesses symptoms experienced in the past 7 days. Participants are asked to respond to the question of "I worry that my condition will get worse" by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 4). A negative change from Baseline (BL) represents a worsening of condition.

End point type	Secondary

End point timeframe:

Week 52, 24M DFS FU, 36M DFS FU,48M DFS FU, 54M DFS FU

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 statistics was planned for this endpoint

End point values	ITT pazopanib 600 mg	ITT placebo 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	571	564		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 (n = 425, 402)	0.01 (± 0.054)	0.09 (± 0.055)		
24M DFS FU (n = 338, 340)	0.11 (± 0.056)	0.16 (± 0.056)		
36M DFS FU (n = 296, 291)	0.13 (± 0.059)	0.12 (± 0.059)		
48M DFS FU (n = 146, 141)	0.08 (± 0.075)	0.20 (± 0.076)		
54M DFS FU (n = 60, 66)	0.04 (± 0.090)	0.24 (± 0.087)		

Statistical analyses

Statistical analysis title	FACT FKSI-19 (600 mg) DRS-E score - W52
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.238
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52)
Point estimate	-0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.205
upper limit	0.051

Statistical analysis title	FACT FKSI-19 (600 mg) DRS-E score - 24M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.442
Method	analysis of covariance
Parameter estimate	Mean Difference (24M DFS FU)
Point estimate	-0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.185
upper limit	0.081

Statistical analysis title	FACT FKSI-19 (600 mg) DRS-E score - 36M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.819
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU)
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.125
upper limit	0.158

Statistical analysis title	FACT FKSI-19 (600 mg) DRS-E score - 48M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.223
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU)
Point estimate	-0.119
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.311
upper limit	0.073

Statistical analysis title	FACT FKSI-19 (600 mg) DRS-E score - 54M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU)
Point estimate	-0.203
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.435
upper limit	0.028

Secondary: Health-related quality of life (HRQoL) with pazopanib 600 mg daily initial dose vs. placebo assessed using NCCN/FACT FKSI-19 Scale Treatment Side Effects (TSE) Domain Score

End point title	Health-related quality of life (HRQoL) with pazopanib 600 mg daily initial dose vs. placebo assessed using NCCN/FACT FKSI-19 Scale Treatment Side Effects (TSE) Domain Score[9]

End point description:

Health outcome and quality of life as measured by NCCN/FACT FKSI-19 questionnaire. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. The TSE domain assesses side effects experienced in the past 7 days. Participants are asked to respond to 3 questions ("I have nausea," "I have diarrhea," and "I am bothered by side effects of treatment") by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 12). Higher scores represent better health.

End point type	Secondary

End point timeframe:

Week 52, 24M DFS FU, 36M DFS FU,48M DFS FU, 54M DFS FU

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 statistics was planned for this endpoint

End point values	ITT pazopanib 600 mg	ITT placebo 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	571	564		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 (n = 426, 404)	-1.73 (± 0.101)	-0.34 (± 0.103)		
24M DFS FU (n = 338, 341)	0.12 (± 0.061)	0.01 (± 0.060)		
36M DFS FU (n = 299, 292)	0.05 (± 0.067)	-0.03 (± 0.067)		
48M DFS FU (n = 146, 140)	-0.04 (± 0.087)	-0.01 (± 0.088)		

54M DFS FU (n = 61, 66)	0.07 (± 0.089)	0.09 (± 0.086)		

Statistical analyses

Statistical analysis title	FACT FKSI-19 (600 mg) TSE score - W52
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52)
Point estimate	-1.394
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.66
upper limit	-1.129

Statistical analysis title	FACT FKSI-19 (600 mg) TSE score - 24M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083
Method	analysis of covariance
Parameter estimate	Mean difference (24M DFS FU)
Point estimate	0.117
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.249

Statistical analysis title	FACT FKSI-19 (600 mg) TSE score - 36M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg

Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.307
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU)
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.074
upper limit	0.236

Statistical analysis title	FACT FKSI-19 (600 mg) TSE score - 48M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.796
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU)
Point estimate	-0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.249
upper limit	0.191

Statistical analysis title	FACT FKSI-19 (600 mg) TSE score - 54M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.885
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU)
Point estimate	-0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.237
upper limit	0.205

Secondary: Health-related quality of life (HRQoL) with pazopanib 600 mg daily

initial dose vs. placebo assessed using NCCN/FACT FKSI-19 Scale Functional Well Being (FWB) Domain Score

End point title	Health-related quality of life (HRQoL) with pazopanib 600 mg daily initial dose vs. placebo assessed using NCCN/FACT FKSI-19 Scale Functional Well Being (FWB) Domain Score[10]

End point description:

Health outcome and quality of life as measured by NCCN/FACT FKSI-19 questionnaire. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. The FWB domain assesses well being in the past 7 days. Participants are asked to respond to 3 questions ("I am able to work," "I am able to enjoy life," and "I am content with the quality of my life now") by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 12). Higher scores represent better health.

End point type	Secondary

End point timeframe:

Week 52, 24M DFS FU, 36M DFS FU,48M DFS FU, 54M DFS FU

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 statistics was planned for this endpoint

End point values	ITT pazopanib 600 mg	ITT placebo 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	571	564		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 (n = 426, 406)	0.06 (± 0.153)	0.33 (± 0.155)		
24M DFS FU (n = 339, 341)	0.39 (± 0.168)	0.32 (± 0.168)		
36M DFS FU (n = 299, 293)	0.43 (± 0.177)	0.24 (± 0.178)		
48M DFS FU (n = 146, 141)	0.51 (± 0.219)	0.42 (± 0.222)		
54M DFS FU (n = 61, 66)	0.31 (± 0.308)	0.59 (± 0.299)		

Statistical analyses

Statistical analysis title	FACT FKSI-19 (600 mg) FWB score - W52
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.143
Method	analysis of covariance
Parameter estimate	Mean Differencec (Week 52)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.633
upper limit	0.092

Statistical analysis title	FACT FKSI-19 (600 mg) FWB score - 24M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.736
Method	analysis of covariance
Parameter estimate	Mean Difference (24M DFS FU)
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.336
upper limit	0.475

Statistical analysis title	FACT FKSI-19 (600 mg) FWB score - 36M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.397
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU)
Point estimate	0.188
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.247
upper limit	0.623

Statistical analysis title	FACT FKSI-19 (600 mg) FWB score - 48M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.781
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU)
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.488
upper limit	0.649

Statistical analysis title	FACT FKSI-19 (600 mg) FWB score - 54M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.503
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU)
Point estimate	-0.278
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.094
upper limit	0.539

Secondary: Health-related quality of life (HRQoL) with pazopanib 600 mg daily initial dose vs. placebo assessed using EuroQoL-5D (EQ-5D) score

End point title	Health-related quality of life (HRQoL) with pazopanib 600 mg daily initial dose vs. placebo assessed using EuroQoL-5D (EQ-5D) score[11]

End point description:

Health outcome and quality of life measured by EQ-5D thermometer (thermo) score and EQ-5D utility index (UI) score. The EQ-5D is a participant-answered questionnaire measuring 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D has two separate components: utility score and thermometer score. The EQ-5D total utility score ranges from 0 (worst health state) to 1 (perfect health state); 1 reflects the best outcome. The thermometer score ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

End point type	Secondary

End point timeframe:

Week 52, 24M DFS FU, 36M DFS FU, 48M DFS FU, 54M DFS FU

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 statistics was planned for this endpoint

End point values	ITT pazopanib 600 mg	ITT placebo 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	571	564		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 thermo. score (n=417,399)	0.713 (± 0.858)	1.430 (± 0.868)		
24M DFS FU thermo. score (n = 328, 334)	3.356 (± 0.882)	3.641 (± 0.877)		
36M DFS FU thermo. score (n = 288, 287)	3.640 (± 0.882)	2.459 (± 0.883)		
48M DFS FU thermo. score (n = 144, 141)	3.909 (± 1.014)	3.184 (± 1.015)		

54M DFS FU thermo. score (n = 60, 65)	3.076 (± 1.607)	1.053 (± 1.560)		
Week 52 UI score (n = 419, 401)	-0.019 (± 0.009)	-0.001 (± 0.009)		
24M DFS FU UI score (n = 334, 337)	-0.004 (± 0.010)	0.016 (± 0.010)		
36M DFS FU UI score (n =294, 288)	0.002 (± 0.011)	-0.008 (± 0.011)		
48M DFS FU UI score (n = 144, 141)	-0.002 (± 0.013)	0.008 (± 0.013)		
54M DFS FU UI score (n = 61, 65)	0.004 (± 0.017)	-0.013 (± 0.017)		

Statistical analyses

Statistical analysis title	EQ-5D (600 mg) thermo. score - W52
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52 thermo)
Point estimate	-0.717
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.751
upper limit	1.318

Statistical analysis title	EQ-5D (600 mg) thermo. score - 24M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.788
Method	analysis of covariance
Parameter estimate	Mean Difference (24M DFS FU- thermo)
Point estimate	-0.285
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.358
upper limit	1.788

Statistical analysis title	EQ-5D (600 mg) thermo. score - 36M DFS FU

Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU- thermo)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.901
upper limit	3.262

Statistical analysis title	EQ-5D (600 mg) thermo. score - 48M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU - thermo)
Point estimate	0.725
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.779
upper limit	3.229

Statistical analysis title	EQ-5D (600 mg) thermo. score - 54M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.346
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU - thermo)
Point estimate	2.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.205
upper limit	6.251

Statistical analysis title	EQ-5D (600 mg) UI score - W52
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52 - UI)
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.004

Statistical analysis title	EQ-5D (600 mg) UI score - 24M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	analysis of covariance
Parameter estimate	Mean Difference (24M DFS FU - UI)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.044
upper limit	0.003

Statistical analysis title	EQ-5D (600 mg) UI score - 36M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU - UI)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.037

Statistical analysis title	EQ-5D (600 mg) UI score - 48M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU - UI)
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.043
upper limit	0.024

Statistical analysis title	EQ-5D(600 mg) UI score - 54M DFS FU
Comparison groups	ITT pazopanib 600 mg v ITT placebo 600 mg
Number of subjects included in analysis	1135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.473
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU - UI)
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.029
upper limit	0.063

Secondary: Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using National Comprehensive Cancer Network (NCCN)/FACT FKSI-19 total score

End point title	Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using National Comprehensive Cancer Network (NCCN)/FACT FKSI-19 total score

End point description:

Health outcome and quality of life measured by NCCN/FACT FKSI-19 questionnaire for ITT ALL. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. The total score assesse for all 4 symptoms (FKSI-DRS-P, FKSI-DRS-E, FKSI-TSE, FKSI-F/WB DRS-P) experienced in the past 7 days for the ITT ALL group. Participants are asked to respond to 12 questions ("I have a lack of energy," "I feel pain," for example) by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 48). Higher scores represent better health.

End point type	Secondary

End point timeframe:
Week 52, 24M DFS FU, 36M DFS FU, 48M DFS FU, 54M DFS FU

End point values	ITT All - pazopanib	ITT All - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	769	769		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 (n = 575, 554)	-4.01 (± 0.385)	-0.47 (± 0.388)		
24M DFS FU (n = 462, 458)	0.23 (± 0.361)	0.33 (± 0.362)		
36M DFS FU (n = 405, 392)	0.16 (± 0.385)	-0.07 (± 0.389)		
48M DFS FU (n = 244, 232)	0.47 (± 0.421)	0.39 (± 0.427)		
54M DFS FU (n = 156, 153)	0.27 (± 0.505)	-0.14 (± 0.509)		

Statistical analyses

Statistical analysis title	FACT FKSI-19 (ITT All) total score - W52
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52)
Point estimate	-3.536
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.466
upper limit	-2.606

Statistical analysis title	FACT FKSI-19 (ITT All) total score - 24M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.812
Method	analysis of covariance
Parameter estimate	Mean difference (24M DFS FU)
Point estimate	-0.102

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.942
upper limit	0.738

Statistical analysis title	FACT FKSI-19 (ITT All) total score - 36M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.621
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU)
Point estimate	0.233
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	1.155

Statistical analysis title	FACT FKSI-19 (ITT All) total score - 48M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.878
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU)
Point estimate	0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.959
upper limit	1.122

Statistical analysis title	FACT FKSI-19 (ITT All) total score - 54M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo

Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.533
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU)
Point estimate	0.412
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.887
upper limit	1.712

Secondary: Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using National Comprehensive Cancer Network (NCCN)/FACT FKSI-19 Scale Disease-related Symptoms-physical (DRS-P) Domain score

End point title	Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using National Comprehensive Cancer Network (NCCN)/FACT FKSI-19 Scale Disease-related Symptoms-physical (DRS-P) Domain score

End point description:

Health outcome and quality of life measured by NCCN/FACT FKSI-19 questionnaire for ITT ALL. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. The DRS-P domain assesses symptoms experienced in the past 7 days. Participants are asked to respond to 12 questions ("I have a lack of energy," "I feel pain," for example) by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 48). Higher scores represent better health.

End point type	Secondary

End point timeframe:

Week 52, 24M DFS FU, 36M DFS FU, 48M DFS FU, 54M DFS FU

End point values	ITT All - pazopanib	ITT All - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	769	769		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 (n = 579, 559)	-2.03 (± 0.235)	-0.51 (± 0.237)		
24M DFS FU (n = 467, 460)	-0.24 (± 0.232)	-0.25 (± 0.233)		
36M DFS FU (n = 412, 395)	-0.41 (± 0.247)	-0.45 (± 0.250)		
48M DFS FU (n = 248, 233)	-0.25 (± 0.270)	-0.19 (± 0.275)		
54M DFS FU (n =157, 153)	-0.23 (± 0.329)	-0.68 (± 0.333)		

Statistical analyses

Statistical analysis title	FACT FKSI-19 (ITT All) DRS-P score - W52
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52)
Point estimate	-1.515
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.078
upper limit	-0.952

Statistical analysis title	FACT FKSI-19 (ITT All) DRS-P score - 24M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.961
Method	analysis of covariance
Parameter estimate	Mean Difference (24M DFS FU)
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.534
upper limit	0.561

Statistical analysis title	FACT FKSI-19 (ITT All) DRS-P score - 36M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.888
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.555
upper limit	0.641

Statistical analysis title	FACT FKSI-19 (ITT All) DRS-P score - 48M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.858
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU)
Point estimate	-0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.736
upper limit	0.614

Statistical analysis title	FACT FKSI-19 (ITT All) DRS-P score - 54M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU)
Point estimate	0.452
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.404
upper limit	1.309

Secondary: Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using National Comprehensive Cancer Network (NCCN)/FACT FKSI-19 Scale Disease-related Symptoms-emotional (DRS-E) Domain Score

End point title	Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using National Comprehensive Cancer Network (NCCN)/FACT FKSI-19 Scale Disease-related Symptoms-emotional (DRS-E) Domain Score

End point description:

Health outcome and quality of life measured by NCCN/FACT FKSI-19 questionnaire for ITT ALL. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. The DRS-E domain assesses symptoms experienced in the past 7 days. Participants are asked to respond to the question of "I worry that my condition will get worse" by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 4). A negative change from Baseline (BL) represents a worsening of condition.

End point type	Secondary

End point timeframe:
Week 52, 24M DFS FU, 36M DFS FU, 48M DFS FU, 54M DFS FU

End point values	ITT All - pazopanib	ITT All - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	769	769		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 (n = 578, 555)	0.04 (± 0.045)	0.14 (± 0.046)		
24M DFS FU (n = 465, 458)	0.15 (± 0.048)	0.19 (± 0.048)		
36M DFS FU (n = 407, 393)	0.19 (± 0.050)	0.15 (± 0.051)		
48M DFS FU (n = 246, 243)	0.16 (± 0.059)	0.20 (± 0.060)		
54M DFS FU (n = 156, 153)	0.16 (± 0.065)	0.17 (± 0.066)		

Statistical analyses

Statistical analysis title	FACT FKSI-19 (ITT All) DRS-E score - W52
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52)
Point estimate	-0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.211
upper limit	0.004

Statistical analysis title	FACT FKSI-19 (ITT All) DRS-E score - 24M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.487
Method	analysis of covariance
Parameter estimate	Mean Difference (24M DFS FU)
Point estimate	-0.041

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.155
upper limit	0.074

Statistical analysis title	FACT FKSI-19 (ITT All) DRS-E score - 36M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.885
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU)
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.085
upper limit	0.16

Statistical analysis title	FACT FKSI-19 (ITT All) DRS-E score - 48M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.676
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU)
Point estimate	-0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.183
upper limit	0.119

Statistical analysis title	FACT FKSI-19 (ITT All) DRS-E score - 54M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo

Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.859
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU)
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.183
upper limit	0.153

Secondary: Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using National Comprehensive Cancer Network (NCCN)/FACT FKSI-19 Scale Treatment Side Effects (TSE) Domain Score

End point title	Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using National Comprehensive Cancer Network (NCCN)/FACT FKSI-19 Scale Treatment Side Effects (TSE) Domain Score

End point description:

Health outcome and quality of life measured by NCCN/FACT FKSI-19 questionnaire for ITT ALL. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. The TSE domain assesses side effects experienced in the past 7 days. Participants are asked to respond to 3 questions ("I have nausea," "I have diarrhea," and "I am bothered by side effects of treatment") by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 12). Higher scores represent better health.

End point type	Secondary

End point timeframe:

Week 52, 24M DFS FU, 36M DFS FU, 48M DFS FU, 54M DFS FU

End point values	ITT All - pazopanib	ITT All - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	769	769		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 (n = 578, 557)	-1.86 (± 0.089)	-0.33 (± 0.090)		
24M DFS FU (n = 465, 460)	0.12 (± 0.052)	0.04 (± 0.052)		
36M DFS FU (n = 411, 394)	0.11 (± 0.057)	-0.02 (± 0.058)		
48M DFS FU (n = 247, 232)	0.05 (± 0.065)	-0.00 (± 0.066)		
54M DFS FU (n = 157, 153)	0.09 (± 0.074)	0.03 (± 0.074)		

Statistical analyses

Statistical analysis title	FACT FKSI-19 (ITT All) TSE score - W52
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	analysis of covariance
Parameter estimate	Mean Diffeence (Week 52)
Point estimate	-1.535
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.769
upper limit	-1.3

Statistical analysis title	FACT FKSI-19 (ITT All) TSE score - 24M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127
Method	analysis of covariance
Parameter estimate	Mean Diffeence (24M DFS FU)
Point estimate	0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.202

Statistical analysis title	FACT FKSI-19 (ITT All) TSE score - 36M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.069
Method	analysis of covariance
Parameter estimate	Mean Diffeence (36M DFS FU)
Point estimate	0.123
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.009
upper limit	0.255

Statistical analysis title	FACT FKSI-19 (ITT All) TSE score - 48M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.544
Method	analysis of covariance
Parameter estimate	Mean Diffeence (48M DFS FU)
Point estimate	0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.208

Statistical analysis title	FACT FKSI-19 (ITT All) TSE score - 54M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.518
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU)
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.124
upper limit	0.246

Secondary: Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using National Comprehensive Cancer Network (NCCN)/FACT FKSI-19 Scale Functional Well Being (FWB) Domain Score

End point title	Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using National Comprehensive Cancer Network (NCCN)/FACT FKSI-19 Scale Functional Well Being (FWB) Domain Score

End point description:

Health outcome and quality of life measured by NCCN/FACT FKSI-19 questionnaire for ITT ALL. The FKSI-19 is a disease-specific instrument that measures disease and treatment-related symptoms specifically in renal cancer patients in 4 domains. The FWB domain assesses well being in the past 7 days. Participants are asked to respond to 3 questions ("I am able to work," "I am able to enjoy life," and "I am content with the quality of my life now") by using a 5-point scale (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much; possible total domain score of 0 to 12). Higher scores represent better health.

End point type	Secondary

End point timeframe:
Week 52, 24M DFS FU, 36M DFS FU, 48M DFS FU, 54M DFS FU

End point values	ITT All - pazopanib	ITT All - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	769	769		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 (n = 579, 559)	-0.08 (± 0.134)	0.30 (± 0.136)		
24M DFS FU (n = 467, 460)	0.30 (± 0.147)	0.41 (± 0.147)		
36M DFS FU (n = 411, 395)	0.3 (± 0.151)	0.29 (± 0.153)		
48M DFS FU (n =247, 243)	0.50 (± 0.179)	0.38 (± 0.183)		
54M DFS FU (n = 157, 153)	0.39 (± 0.206)	0.44 (± 0.208)		

Statistical analyses

Statistical analysis title	FACT FKSI-19 (ITT All) FWB score - W52
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.022
Method	analysis of covariance
Parameter estimate	Mean Diffeence (Week 52)
Point estimate	-0.374
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.695
upper limit	-0.053

Statistical analysis title	FACT FKSI-19 (ITT All) FWB score - 24M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.567
Method	analysis of covariance
Parameter estimate	Mean Diffeence (24M DFS FU)
Point estimate	-0.104

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.462
upper limit	0.253

Statistical analysis title	FACT FKSI-19 (ITT All) FWB score - 36M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.706
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU)
Point estimate	0.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.302
upper limit	0.446

Statistical analysis title	FACT FKSI-19 (ITT All) FWB score - 48M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.612
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU)
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.343
upper limit	0.583

Statistical analysis title	FACT FKSI-19 (ITT All) FWB score - 54M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo

Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU)
Point estimate	-0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.587
upper limit	0.496

Secondary: Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using EuroQoL-5D (EQ-5D) score

End point title	Health-related quality of life (HRQoL) with pazopanib vs. placebo for ITT ALL assessed using EuroQoL-5D (EQ-5D) score

End point description:

Health outcome and quality of life measured by using EQ-5D thermometer score and EQ-5D utility index (UI) score. The EQ-5D is a participant-answered questionnaire measuring 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D has two separate components: utility score and thermometer score. The EQ-5D total utility score ranges from 0 (worst health state) to 1 (perfect health state); 1 reflects the best outcome. The thermometer score ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

End point type	Secondary

End point timeframe:

Week 52, 24M DFS FU, 36M DFS FU, 48M DFS FU, 54M DFS FU

End point values	ITT All - pazopanib	ITT All - placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	769	769		
Units: scores on a scale				
least squares mean (standard error)				
Week 52 thermo. (n = 568, 546)	0.744 (± 0.733)	2.859 (± 0.742)		
24M DFS FU thermo. (n = 452, 450)	4.043 (± 0.741)	4.296 (± 0.743)		
36M DFS FU thermo. (n = 398, 387)	3.997 (± 0.774)	3.150 (± 0.781)		
48M DFS FU thermo. (n = 245, 232)	4.683 (± 0.863)	4.552 (± 0.877)		
54M DFS FU thermos. (n = 155, 149)	3.650 (± 1.028)	3.249 (± 1.043)		
Week 52 UI score (n = 571, 548)	-0.023 (± 0.008)	0.003 (± 0.008)		
24M DFS FU UI score (n = 460, 453)	0.001 (± 0.008)	0.017 (± 0.008)		
36M DFS FU UI score (n = 404, 387)	0.004 (± 0.009)	-0.004 (± 0.009)		

48M DFS FU UI score (n = 244, 231) 54M DFS FU UI score (n = 156, 147)	-0.004 (± 0.010) -0.004 (± 0.012)	0.010 (± 0.010) 0.003 (± 0.012)		

Statistical analyses

Statistical analysis title	EQ-5D (ITT All) thermo. score - W52
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52 - thermo.)
Point estimate	-2.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.872
upper limit	-0.359

Statistical analysis title	EQ-5D (ITT All) thermo. score - 24M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.778
Method	analysis of covariance
Parameter estimate	Mean Difference (24M DFS FU - thermo)
Point estimate	-0.253
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.014
upper limit	1.508

Statistical analysis title	EQ-5D (ITT All) thermo. score - 36M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo

Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.376
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU - thermo)
Point estimate	0.847
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	2.724

Statistical analysis title	EQ-5D (ITT All) thermo. score - 48M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.905
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU - thermo)
Point estimate	0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.032
upper limit	2.294

Statistical analysis title	EQ-5D (ITT All) thermo. score - 54M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.768
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU - thermo)
Point estimate	0.401
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.269
upper limit	3.071

Statistical analysis title	EQ-5D (ITT All) UI score - W52

Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	analysis of covariance
Parameter estimate	Mean Difference (Week 52 - UI)
Point estimate	-0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.044
upper limit	-0.007

Statistical analysis title	EQ-5D (ITT All) UI score - 24M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	analysis of covariance
Parameter estimate	Mean Difference (24M DFS FU - UI)
Point estimate	-0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.005

Statistical analysis title	EQ-5D (ITT All) UI score - 36M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	analysis of covariance
Parameter estimate	Mean Difference (36M DFS FU - UI)
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.03

Statistical analysis title	EQ-5D (ITT All) UI score - 48M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276
Method	analysis of covariance
Parameter estimate	Mean Difference (48M DFS FU - UI)
Point estimate	-0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.011

Statistical analysis title	EQ-5D (ITT All) UI score - 54M DFS FU
Comparison groups	ITT All - pazopanib v ITT All - placebo
Number of subjects included in analysis	1538
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.665
Method	analysis of covariance
Parameter estimate	Mean Difference (54M DFS FU - UI)
Point estimate	-0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.024

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	ITT pazopanib 800 mg

Reporting group description:

Pazopanib 800 mg daily dose based on safety evaluation. Complete treatment is 12 months.

Reporting group title	ITT placebo 800 mg

Reporting group description:

Placebo matching pazopanib 800 mg daily. Complete treatment is 12 months.

Reporting group title	ITT pazopanib 600 mg

Reporting group description:

ITT pazopanib 600 mg Pazopanib 600 mg daily initial dose for 8-12 weeks. Dose can be escalated to 800 mg daily based on safety evaluation. Complete treatment is 12 months.

Reporting group title	ITT placebo 600 mg

Reporting group description:

Placebo matching pazopanib 600 mg daily. Complete treatment is 12 months.

Reporting group title	ITT All - Pazopanib

Reporting group description:

All randomized subjects with a scheduled initial dose of 600 or 800 mg daily pazopanib.

Reporting group title	ITT All - Placebo

Reporting group description:

All randomized subjects with a scheduled initial dose of 600 or 800 mg daily placebo.

Serious adverse events	ITT pazopanib 800 mg	ITT placebo 800 mg	ITT pazopanib 600 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 198 (22.22%)	14 / 204 (6.86%)	123 / 568 (21.65%)
number of deaths (all causes)	1	0	3
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Biliary neoplasm			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Breast cancer			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Gallbladder cancer			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Ovarian epithelial cancer			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Papillary thyroid cancer			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Prostate cancer			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Thyroid cancer			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour thrombosis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 198 (1.52%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	2 / 198 (1.01%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Venous thrombosis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Pyrexia			
subjects affected / exposed	1 / 198 (0.51%)	2 / 204 (0.98%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung transplant rejection			
subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	0 / 568 (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

Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Menorrhagia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	2 / 568 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	0 / 568 (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
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Panic disorder			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 198 (7.58%)	0 / 204 (0.00%)	51 / 568 (8.98%)
occurrences causally related to treatment / all	11 / 11	0 / 0	38 / 40
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	12 / 568 (2.11%)
occurrences causally related to treatment / all	1 / 1	0 / 0	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilirubin conjugated increased			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	3 / 568 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	4 / 568 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic enzymes increased			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Transaminases increased			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	3 / 568 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	0 / 568 (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
Fall			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Muscle rupture			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Patella fracture			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			
subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	0 / 568 (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
Thermal burn			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Wound dehiscence			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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 myocardial infarction			
subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	0 / 568 (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
Angina pectoris			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Atrial fibrillation			

subjects affected / exposed	0 / 198 (0.00%)	2 / 204 (0.98%)	0 / 568 (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
Atrioventricular block second degree			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Myocardial infarction			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Nervous system disorders			
Brain hypoxia			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral haemorrhage			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	2 / 568 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral ischaemia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Dizziness			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Presyncope			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	2 / 568 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Polycythaemia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	2 / 568 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Macular hole			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Retinal detachment			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	2 / 568 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal tear			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 198 (1.01%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal haemorrhage			
subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	0 / 568 (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
Diarrhoea			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	3 / 568 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer perforation			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			

subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	0 / 568 (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
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	0 / 568 (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
Large intestine perforation			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	2 / 568 (0.35%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	2 / 568 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	0 / 568 (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
Biliary colic			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Cholecystitis			
subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Drug-induced liver injury			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	5 / 198 (2.53%)	0 / 204 (0.00%)	3 / 568 (0.53%)
occurrences causally related to treatment / all	2 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular injury			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver injury			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	2 / 568 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Proteinuria			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Renal failure			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	2 / 568 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal tubular necrosis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Flank pain			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral disc protrusion			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
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			
Abdominal wall abscess			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal abscess			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Bacterial sepsis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Bronchitis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Bronchitis viral			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Clostridium difficile infection			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Diabetic gangrene			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Erysipelas			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Gastroenteritis			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Gastroenteritis salmonella			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Pneumonia			

subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary tuberculosis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Respiratory tract infection			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Sepsis			
subjects affected / exposed	0 / 198 (0.00%)	1 / 204 (0.49%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superinfection bacterial			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Urinary tract infection			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Urosepsis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Viral infection			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	3 / 568 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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
Hypertriglyceridaemia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	0 / 568 (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
Hyperuricaemia			
subjects affected / exposed	0 / 198 (0.00%)	0 / 204 (0.00%)	1 / 568 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 204 (0.00%)	0 / 568 (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

Serious adverse events	ITT placebo 600 mg	ITT All - Pazopanib	ITT All - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 558 (9.68%)	167 / 766 (21.80%)	68 / 762 (8.92%)
number of deaths (all causes)	0	4	0
number of deaths resulting from adverse events	0	1	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary neoplasm			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder cancer			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 558 (0.18%)	1 / 766 (0.13%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Ovarian epithelial cancer			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Papillary thyroid cancer			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 558 (0.36%)	0 / 766 (0.00%)	2 / 762 (0.26%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Tumour thrombosis			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 558 (0.00%)	4 / 766 (0.52%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 558 (0.18%)	3 / 766 (0.39%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	1 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (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
Hypotension			

subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Hypovolaemic shock			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Thrombophlebitis			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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			
Chest pain			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	2 / 762 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Lung transplant rejection			
subjects affected / exposed	0 / 558 (0.00%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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			
Alveolitis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Dyspnoea			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (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
Pleural effusion			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Pleurisy			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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	3 / 558 (0.54%)	0 / 766 (0.00%)	4 / 762 (0.52%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			

subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic disorder			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Suicide attempt			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 558 (0.36%)	66 / 766 (8.62%)	2 / 762 (0.26%)
occurrences causally related to treatment / all	1 / 1	49 / 51	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 558 (0.00%)	13 / 766 (1.70%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	10 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilirubin conjugated increased			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Blood bilirubin increased			
subjects affected / exposed	0 / 558 (0.00%)	3 / 766 (0.39%)	0 / 762 (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 glucose increased			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Hepatic enzyme increased			

subjects affected / exposed	0 / 558 (0.00%)	4 / 766 (0.52%)	0 / 762 (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
International normalised ratio increased			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Lipase increased			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Pancreatic enzymes increased			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 558 (0.00%)	3 / 766 (0.39%)	0 / 762 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 558 (0.00%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle rupture			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			

subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Pubis fracture			
subjects affected / exposed	0 / 558 (0.00%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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 myocardial infarction			
subjects affected / exposed	0 / 558 (0.00%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	3 / 762 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Bradycardia			
subjects affected / exposed	2 / 558 (0.36%)	0 / 766 (0.00%)	2 / 762 (0.26%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Cardiomyopathy			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Ventricular tachycardia			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain hypoxia			

subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Seizure			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Syncope			
subjects affected / exposed	2 / 558 (0.36%)	2 / 766 (0.26%)	2 / 762 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	2 / 558 (0.36%)	0 / 766 (0.00%)	2 / 762 (0.26%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 558 (0.36%)	1 / 766 (0.13%)	2 / 762 (0.26%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Polycythaemia			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Thrombocytopenia			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Eye disorders			
Macular hole			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Retinal detachment			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (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
Retinal tear			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Visual impairment			

subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 558 (0.00%)	3 / 766 (0.39%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal haemorrhage			
subjects affected / exposed	0 / 558 (0.00%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 558 (0.00%)	4 / 766 (0.52%)	0 / 762 (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
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Gastric ulcer perforation			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Haematochezia			

subjects affected / exposed	0 / 558 (0.00%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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 / 558 (0.00%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Pancreatitis			
subjects affected / exposed	0 / 558 (0.00%)	3 / 766 (0.39%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (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
Vomiting			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	0 / 558 (0.00%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary colic			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	3 / 558 (0.54%)	1 / 766 (0.13%)	4 / 762 (0.52%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	2 / 558 (0.36%)	0 / 766 (0.00%)	2 / 762 (0.26%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Hepatic function abnormal			
subjects affected / exposed	1 / 558 (0.18%)	8 / 766 (1.04%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	1 / 1	5 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular injury			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Liver disorder			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Liver injury			

subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Rash			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 558 (0.36%)	1 / 766 (0.13%)	2 / 762 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Nephrotic syndrome			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Renal colic			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal tubular necrosis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Ureterolithiasis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Back pain			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 558 (0.00%)	2 / 766 (0.26%)	0 / 762 (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

Intervertebral disc protrusion			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Osteoarthritis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Anal abscess			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Appendiceal abscess			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Bacterial sepsis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Bronchitis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Bronchitis viral			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Clostridium difficile infection			

subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Cystitis			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic gangrene			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	3 / 558 (0.54%)	0 / 766 (0.00%)	3 / 762 (0.39%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Infected skin ulcer			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Peritonsillar abscess			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 558 (0.18%)	1 / 766 (0.13%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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 tract infection			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superinfection bacterial			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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 tract infection			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Viral infection			
subjects affected / exposed	1 / 558 (0.18%)	1 / 766 (0.13%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 558 (0.00%)	4 / 766 (0.52%)	0 / 762 (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
Diabetes mellitus			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Electrolyte imbalance			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Hyperkalaemia			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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
Hypertriglyceridaemia			
subjects affected / exposed	1 / 558 (0.18%)	0 / 766 (0.00%)	1 / 762 (0.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (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 / 558 (0.00%)	1 / 766 (0.13%)	0 / 762 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ITT pazopanib 800 mg	ITT placebo 800 mg	ITT pazopanib 600 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	194 / 198 (97.98%)	147 / 204 (72.06%)	541 / 568 (95.25%)
Vascular disorders			
Hypertension			
subjects affected / exposed	108 / 198 (54.55%)	30 / 204 (14.71%)	294 / 568 (51.76%)
occurrences (all)	137	37	367
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	24 / 198 (12.12%)	12 / 204 (5.88%)	79 / 568 (13.91%)
occurrences (all)	28	19	96
Fatigue			
subjects affected / exposed	74 / 198 (37.37%)	53 / 204 (25.98%)	222 / 568 (39.08%)
occurrences (all)	90	62	255
Mucosal inflammation			
subjects affected / exposed	21 / 198 (10.61%)	5 / 204 (2.45%)	46 / 568 (8.10%)
occurrences (all)	22	5	58
Oedema peripheral			
subjects affected / exposed	12 / 198 (6.06%)	10 / 204 (4.90%)	17 / 568 (2.99%)
occurrences (all)	10	10	17
Pyrexia			
subjects affected / exposed	13 / 198 (6.57%)	7 / 204 (3.43%)	21 / 568 (3.70%)
occurrences (all)	18	6	17
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 198 (7.58%)	12 / 204 (5.88%)	51 / 568 (8.98%)
occurrences (all)	14	12	56
Dysphonia			
subjects affected / exposed	14 / 198 (7.07%)	2 / 204 (0.98%)	55 / 568 (9.68%)
occurrences (all)	17	2	65
Dyspnoea			
subjects affected / exposed	17 / 198 (8.59%)	10 / 204 (4.90%)	35 / 568 (6.16%)
occurrences (all)	16	21	37
Epistaxis			
subjects affected / exposed	16 / 198 (8.08%)	5 / 204 (2.45%)	47 / 568 (8.27%)
occurrences (all)	24	5	52

Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 198 (5.05%)	8 / 204 (3.92%)	29 / 568 (5.11%)
occurrences (all)	22	9	28
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	51 / 198 (25.76%)	11 / 204 (5.39%)	146 / 568 (25.70%)
occurrences (all)	61	14	165
Aspartate aminotransferase increased			
subjects affected / exposed	48 / 198 (24.24%)	5 / 204 (2.45%)	129 / 568 (22.71%)
occurrences (all)	55	5	134
Blood bilirubin increased			
subjects affected / exposed	8 / 198 (4.04%)	5 / 204 (2.45%)	32 / 568 (5.63%)
occurrences (all)	13	7	35
Blood creatinine increased			
subjects affected / exposed	14 / 198 (7.07%)	14 / 204 (6.86%)	29 / 568 (5.11%)
occurrences (all)	19	16	36
Platelet count decreased			
subjects affected / exposed	10 / 198 (5.05%)	1 / 204 (0.49%)	32 / 568 (5.63%)
occurrences (all)	14	1	36
Weight decreased			
subjects affected / exposed	10 / 198 (5.05%)	2 / 204 (0.98%)	33 / 568 (5.81%)
occurrences (all)	9	2	32
Nervous system disorders			
Dizziness			
subjects affected / exposed	26 / 198 (13.13%)	17 / 204 (8.33%)	50 / 568 (8.80%)
occurrences (all)	25	20	52
Dysgeusia			
subjects affected / exposed	43 / 198 (21.72%)	5 / 204 (2.45%)	171 / 568 (30.11%)
occurrences (all)	46	7	191
Headache			
subjects affected / exposed	58 / 198 (29.29%)	35 / 204 (17.16%)	139 / 568 (24.47%)
occurrences (all)	75	46	167
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	12 / 198 (6.06%)	0 / 204 (0.00%)	25 / 568 (4.40%)
occurrences (all)	16	0	34
Thrombocytopenia			
subjects affected / exposed	12 / 198 (6.06%)	1 / 204 (0.49%)	22 / 568 (3.87%)
occurrences (all)	13	1	24
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 198 (13.64%)	24 / 204 (11.76%)	85 / 568 (14.96%)
occurrences (all)	37	28	100
Abdominal pain upper			
subjects affected / exposed	18 / 198 (9.09%)	5 / 204 (2.45%)	58 / 568 (10.21%)
occurrences (all)	18	5	67
Constipation			
subjects affected / exposed	17 / 198 (8.59%)	17 / 204 (8.33%)	28 / 568 (4.93%)
occurrences (all)	17	22	27
Diarrhoea			
subjects affected / exposed	129 / 198 (65.15%)	48 / 204 (23.53%)	361 / 568 (63.56%)
occurrences (all)	209	69	550
Dyspepsia			
subjects affected / exposed	17 / 198 (8.59%)	13 / 204 (6.37%)	43 / 568 (7.57%)
occurrences (all)	19	15	49
Flatulence			
subjects affected / exposed	8 / 198 (4.04%)	6 / 204 (2.94%)	32 / 568 (5.63%)
occurrences (all)	8	7	35
Nausea			
subjects affected / exposed	89 / 198 (44.95%)	28 / 204 (13.73%)	226 / 568 (39.79%)
occurrences (all)	133	34	301
Stomatitis			
subjects affected / exposed	23 / 198 (11.62%)	10 / 204 (4.90%)	55 / 568 (9.68%)
occurrences (all)	25	13	63
Vomiting			
subjects affected / exposed	37 / 198 (18.69%)	8 / 204 (3.92%)	95 / 568 (16.73%)
occurrences (all)	51	10	132
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	26 / 198 (13.13%)	6 / 204 (2.94%)	64 / 568 (11.27%)
occurrences (all)	24	6	65
Dry skin			
subjects affected / exposed	14 / 198 (7.07%)	9 / 204 (4.41%)	38 / 568 (6.69%)
occurrences (all)	13	10	40
Hair colour changes			
subjects affected / exposed	90 / 198 (45.45%)	9 / 204 (4.41%)	232 / 568 (40.85%)
occurrences (all)	87	9	233
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	42 / 198 (21.21%)	8 / 204 (3.92%)	103 / 568 (18.13%)
occurrences (all)	51	9	117
Pruritus			
subjects affected / exposed	12 / 198 (6.06%)	17 / 204 (8.33%)	25 / 568 (4.40%)
occurrences (all)	14	17	23
Rash			
subjects affected / exposed	24 / 198 (12.12%)	14 / 204 (6.86%)	63 / 568 (11.09%)
occurrences (all)	36	19	70
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	14 / 198 (7.07%)	5 / 204 (2.45%)	24 / 568 (4.23%)
occurrences (all)	16	6	24
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	24 / 198 (12.12%)	2 / 204 (0.98%)	55 / 568 (9.68%)
occurrences (all)	29	2	53
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 198 (9.09%)	13 / 204 (6.37%)	47 / 568 (8.27%)
occurrences (all)	22	15	53
Back pain			
subjects affected / exposed	29 / 198 (14.65%)	15 / 204 (7.35%)	53 / 568 (9.33%)
occurrences (all)	37	15	55
Muscle spasms			
subjects affected / exposed	13 / 198 (6.57%)	10 / 204 (4.90%)	26 / 568 (4.58%)
occurrences (all)	13	13	30
Myalgia			

subjects affected / exposed	16 / 198 (8.08%)	8 / 204 (3.92%)	39 / 568 (6.87%)
occurrences (all)	17	10	48
Pain in extremity			
subjects affected / exposed	22 / 198 (11.11%)	12 / 204 (5.88%)	42 / 568 (7.39%)
occurrences (all)	24	13	53
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 198 (6.57%)	12 / 204 (5.88%)	27 / 568 (4.75%)
occurrences (all)	13	15	35
Upper respiratory tract infection			
subjects affected / exposed	11 / 198 (5.56%)	7 / 204 (3.43%)	12 / 568 (2.11%)
occurrences (all)	11	8	13
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	42 / 198 (21.21%)	11 / 204 (5.39%)	112 / 568 (19.72%)
occurrences (all)	48	11	123

Non-serious adverse events	ITT placebo 600 mg	ITT All - Pazopanib	ITT All - Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	448 / 558 (80.29%)	735 / 766 (95.95%)	595 / 762 (78.08%)
Vascular disorders			
Hypertension			
subjects affected / exposed	107 / 558 (19.18%)	402 / 766 (52.48%)	137 / 762 (17.98%)
occurrences (all)	137	504	174
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	53 / 558 (9.50%)	103 / 766 (13.45%)	65 / 762 (8.53%)
occurrences (all)	69	124	88
Fatigue			
subjects affected / exposed	144 / 558 (25.81%)	296 / 766 (38.64%)	197 / 762 (25.85%)
occurrences (all)	167	345	229
Mucosal inflammation			
subjects affected / exposed	17 / 558 (3.05%)	67 / 766 (8.75%)	22 / 762 (2.89%)
occurrences (all)	19	80	24
Oedema peripheral			
subjects affected / exposed	29 / 558 (5.20%)	29 / 766 (3.79%)	39 / 762 (5.12%)
occurrences (all)	34	27	44

Pyrexia			
subjects affected / exposed	22 / 558 (3.94%)	34 / 766 (4.44%)	29 / 762 (3.81%)
occurrences (all)	28	35	34
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	52 / 558 (9.32%)	66 / 766 (8.62%)	64 / 762 (8.40%)
occurrences (all)	57	70	69
Dysphonia			
subjects affected / exposed	10 / 558 (1.79%)	69 / 766 (9.01%)	12 / 762 (1.57%)
occurrences (all)	10	82	12
Dyspnoea			
subjects affected / exposed	26 / 558 (4.66%)	52 / 766 (6.79%)	36 / 762 (4.72%)
occurrences (all)	27	53	48
Epistaxis			
subjects affected / exposed	11 / 558 (1.97%)	63 / 766 (8.22%)	16 / 762 (2.10%)
occurrences (all)	22	76	27
Psychiatric disorders			
Insomnia			
subjects affected / exposed	28 / 558 (5.02%)	39 / 766 (5.09%)	36 / 762 (4.72%)
occurrences (all)	30	50	39
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 558 (4.66%)	197 / 766 (25.72%)	37 / 762 (4.86%)
occurrences (all)	36	226	50
Aspartate aminotransferase increased			
subjects affected / exposed	22 / 558 (3.94%)	177 / 766 (23.11%)	27 / 762 (3.54%)
occurrences (all)	25	189	30
Blood bilirubin increased			
subjects affected / exposed	6 / 558 (1.08%)	40 / 766 (5.22%)	11 / 762 (1.44%)
occurrences (all)	7	48	14
Blood creatinine increased			
subjects affected / exposed	32 / 558 (5.73%)	43 / 766 (5.61%)	46 / 762 (6.04%)
occurrences (all)	34	55	50
Platelet count decreased			
subjects affected / exposed	7 / 558 (1.25%)	42 / 766 (5.48%)	8 / 762 (1.05%)
occurrences (all)	11	50	12

Weight decreased			
subjects affected / exposed	7 / 558 (1.25%)	43 / 766 (5.61%)	9 / 762 (1.18%)
occurrences (all)	7	41	9
Nervous system disorders			
Dizziness			
subjects affected / exposed	52 / 558 (9.32%)	76 / 766 (9.92%)	69 / 762 (9.06%)
occurrences (all)	71	77	91
Dysgeusia			
subjects affected / exposed	15 / 558 (2.69%)	214 / 766 (27.94%)	20 / 762 (2.62%)
occurrences (all)	16	237	23
Headache			
subjects affected / exposed	78 / 558 (13.98%)	197 / 766 (25.72%)	113 / 762 (14.83%)
occurrences (all)	97	242	143
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 558 (0.36%)	37 / 766 (4.83%)	2 / 762 (0.26%)
occurrences (all)	3	50	3
Thrombocytopenia			
subjects affected / exposed	6 / 558 (1.08%)	34 / 766 (4.44%)	7 / 762 (0.92%)
occurrences (all)	8	37	9
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	46 / 558 (8.24%)	112 / 766 (14.62%)	70 / 762 (9.19%)
occurrences (all)	59	137	87
Abdominal pain upper			
subjects affected / exposed	18 / 558 (3.23%)	76 / 766 (9.92%)	23 / 762 (3.02%)
occurrences (all)	19	85	24
Constipation			
subjects affected / exposed	38 / 558 (6.81%)	45 / 766 (5.87%)	55 / 762 (7.22%)
occurrences (all)	45	44	67
Diarrhoea			
subjects affected / exposed	139 / 558 (24.91%)	490 / 766 (63.97%)	187 / 762 (24.54%)
occurrences (all)	198	759	267
Dyspepsia			
subjects affected / exposed	17 / 558 (3.05%)	60 / 766 (7.83%)	30 / 762 (3.94%)
occurrences (all)	44	68	59
Flatulence			

subjects affected / exposed	18 / 558 (3.23%)	40 / 766 (5.22%)	24 / 762 (3.15%)
occurrences (all)	18	43	25
Nausea			
subjects affected / exposed	89 / 558 (15.95%)	315 / 766 (41.12%)	117 / 762 (15.35%)
occurrences (all)	112	434	146
Stomatitis			
subjects affected / exposed	23 / 558 (4.12%)	78 / 766 (10.18%)	33 / 762 (4.33%)
occurrences (all)	25	88	38
Vomiting			
subjects affected / exposed	21 / 558 (3.76%)	132 / 766 (17.23%)	29 / 762 (3.81%)
occurrences (all)	24	183	34
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	19 / 558 (3.41%)	90 / 766 (11.75%)	25 / 762 (3.28%)
occurrences (all)	19	89	25
Dry skin			
subjects affected / exposed	32 / 558 (5.73%)	52 / 766 (6.79%)	41 / 762 (5.38%)
occurrences (all)	33	53	43
Hair colour changes			
subjects affected / exposed	28 / 558 (5.02%)	322 / 766 (42.04%)	37 / 762 (4.86%)
occurrences (all)	29	320	38
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	24 / 558 (4.30%)	145 / 766 (18.93%)	32 / 762 (4.20%)
occurrences (all)	28	168	37
Pruritus			
subjects affected / exposed	41 / 558 (7.35%)	37 / 766 (4.83%)	58 / 762 (7.61%)
occurrences (all)	44	37	61
Rash			
subjects affected / exposed	36 / 558 (6.45%)	87 / 766 (11.36%)	50 / 762 (6.56%)
occurrences (all)	37	106	56
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 558 (0.36%)	38 / 766 (4.96%)	7 / 762 (0.92%)
occurrences (all)	2	40	8
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	4 / 558 (0.72%)	79 / 766 (10.31%)	6 / 762 (0.79%)
occurrences (all)	4	82	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	68 / 558 (12.19%)	65 / 766 (8.49%)	81 / 762 (10.63%)
occurrences (all)	80	75	95
Back pain			
subjects affected / exposed	78 / 558 (13.98%)	82 / 766 (10.70%)	93 / 762 (12.20%)
occurrences (all)	114	92	129
Muscle spasms			
subjects affected / exposed	11 / 558 (1.97%)	39 / 766 (5.09%)	21 / 762 (2.76%)
occurrences (all)	11	43	24
Myalgia			
subjects affected / exposed	32 / 558 (5.73%)	55 / 766 (7.18%)	40 / 762 (5.25%)
occurrences (all)	35	65	45
Pain in extremity			
subjects affected / exposed	30 / 558 (5.38%)	64 / 766 (8.36%)	42 / 762 (5.51%)
occurrences (all)	34	77	47
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	40 / 558 (7.17%)	40 / 766 (5.22%)	52 / 762 (6.82%)
occurrences (all)	46	48	61
Upper respiratory tract infection			
subjects affected / exposed	21 / 558 (3.76%)	23 / 766 (3.00%)	28 / 762 (3.67%)
occurrences (all)	27	24	35
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	22 / 558 (3.94%)	154 / 766 (20.10%)	33 / 762 (4.33%)
occurrences (all)	23	171	34

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2011	Protocol Amendment 1 was a country specific amendment for France to include specific requirements 1) regarding potassium assessments and eligibility, 2) Added alert for medications known to be associated with QT prolongation or Torsades de pointes (TdP).
12 August 2011	Protocol Amendment 2 introduced the following changes: 1) Treatment to start at 600 mg for all subjects for 8-12 weeks. Dose escalation to 800 mg based on evaluation of subject's safety and tolerability profile; 2) Revisions in the dose modification guidelines; 3) Addition of pharmacokinetic research; 4) Clarifications on several inclusion/exclusion criteria and screening baseline windows; 5) Clarifications on imaging assessment methods for different anatomic regions; 6) addition of Week 24 visit; and 7) Addition of routine pregnancy tests for female subjects with child-bearing potential.
09 January 2013	Protocol Amendment 3 introduced the following changes: 1) Revisions on study objectives in Section 2 of the Protocol – primary objective is to evaluate pazopanib 600 mg daily initial dose vs. placebo for DFS; secondary objectives are to evaluate i) pazopanib 600 mg daily initial dose vs. placebo, ii) pazopanib vs. placebo in all subjects regardless of initial dose, iii) pazopanib 800 mg daily initial dose vs. placebo; 2) Revisions in Section 9 of the Protocol on statistical hypothesis and sample size reestimations using subjects randomized into 600 mg daily initial dose as the primary analysis population on DFS and OS; 3) Revisions on secondary analyses; 4) Revisions on Section 3 of the Protocol in accordance with revisions in Section 2 and Section 9; 5) In Section 5.2 of the Protocol, clarified scheduled initial dose; 6) In Section 5.9 of the protocol and other relevant sections – clarified criteria for liver toxicity category E and cut-off for total bilirubin fractionation; 7) In Section 6 of the Protocol, clarified concomitant medication collection timing and added caution on concomitant use of simvastatin; 8) Addition of visit Week 6.5 for serum liver test monitoring.
06 August 2015	The primary purpose of Protocol Amendment 4 was to modify the timing of the primary analysis: in an adjuvant setting, where the cure rate model is likely to apply, the power of the study may be reduced if the analysis is not performed until 15-Oct-2016. Therefore, the cut-off date for the analysis was moved earlier, while still requiring the target number of 319 DFS events to be achieved. Major changes included: 1) Change of timing of Primary Analysis to be performed 1 year earlier than planned, following data cut-off on 15-Oct-2015, with an exploratory follow-up analysis of DFS to be performed with a data cut-off of 15-Oct-2016; 2) Change of study physician contact information; 3) Specify the alpha spending function used for type I error control in OS group sequential analysis (first interim analysis at the time of the primary analysis following data cut-off on 15-Oct-2015, and 2nd interim analysis at the time of the follow-up, exploratory DFS analysis following data cut-off on 15-OCT-2016); 4) Addition of PK data analysis section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: