Clinical trial results:
Study VEG108844, A study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma

Summary

EudraCT number	2008-002102-19
Trial protocol	IE GB ES SE NL IT DE
Global end of trial date	24 March 2021

Results information

Result version number	v2 (current)
This version publication date	16 April 2025
First version publication date	06 April 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	108844

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00720941
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis: CPZP034A2301, GlaxoSmithKline: VEG108844

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, 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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare progression-free survival of subjects treated with pazopanib to those treated with sunitinib.

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	14 August 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 51
Country: Number of subjects enrolled	Canada: 46
Country: Number of subjects enrolled	China: 209
Country: Number of subjects enrolled	Germany: 55
Country: Number of subjects enrolled	Ireland: 17
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Japan: 61
Country: Number of subjects enrolled	Korea, Republic of: 68
Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	Sweden: 16
Country: Number of subjects enrolled	Taiwan: 29
Country: Number of subjects enrolled	United Kingdom: 126
Country: Number of subjects enrolled	United States: 336
Worldwide total number of subjects	1110
EEA total number of subjects	184

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)	676
From 65 to 84 years	428
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were stratified based on Karnofsky Performance Scale scores (70 or 80; 90 or 100), Baseline levels of lactate dehydrogenase (>1.5 versus <=1.5 times the upper limit of normal [ULN]), and previous nephrectomy (yes versus no) and were randomized in a 1:1 ratio to receive either pazopanib or sunitinib.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pazopanib 800 mg

Arm description:

Participants were administered pazopanib 800 milligrams (mg) (2 x 400 mg tablets) orally once daily (OD) continuously. Pazopanib was to be taken at least one hour before or at least two hours after a meal. Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	GW786034
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg (2 x 400 mg tablets or 4 x 200 mg tablets) administered orally once daily (continuously) at least 1 hour before or at least 2 hours after a meal.

Arm title	Sunitinib 50 mg

Arm description:

Participants were administered sunitinib 50 mg orally once daily in 6-week cycles (4 weeks of treatment, followed by 2 weeks without treatment). Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.

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

Dosage and administration details:

50 mg administered in 6-week cycles orally once daily with or without food, for 4 weeks of treatment followed by 2 weeks without treatment.

Number of subjects in period 1	Pazopanib 800 mg	Sunitinib 50 mg
Started	557	553
Safety Population	554	548
Completed	485	481
Not completed	72	72
Physician decision	14	12
Consent withdrawn by subject	29	36
Lost to follow-up	20	15
Protocol deviation	1	2
Transitioned to another mechanism of cont. therapy	8	7

Baseline characteristics

Reporting groups	
Reporting group title	Pazopanib 800 mg
Reporting group description:	
Participants were administered pazopanib 800 milligrams (mg) (2 x 400 mg tablets) orally once daily (OD) continuously. Pazopanib was to be taken at least one hour before or at least two hours after a meal. Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.	
Reporting group title	Sunitinib 50 mg
Reporting group description:	
Participants were administered sunitinib 50 mg orally once daily in 6-week cycles (4 weeks of treatment, followed by 2 weeks without treatment). Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.	

Reporting group values	Pazopanib 800 mg	Sunitinib 50 mg	Total
Number of subjects	557	553	1110
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	344	332	676
From 65-84 years	208	220	428
85 years and over	5	1	6
Gender categorical Units: Subjects			
Female	159	138	297
Male	398	415	813
Race/Ethnicity, Customized Units: Subjects			
White	349	358	707
Asian	194	188	382
African American/African Heritage	10	5	15
American Indian or Alaska Native	3	0	3
American Indian or Alaska Native & White	0	1	1
Unknown	1	1	2
GenderNIH Units: Subjects			
Female	159	138	297
Male	398	415	813
AgeContinuous Units: Years			
arithmetic mean	60.9	61.2	
standard deviation	± 10.89	± 10.98	-

End points

End points reporting groups

Reporting group title	Pazopanib 800 mg

Reporting group description:

Participants were administered pazopanib 800 milligrams (mg) (2 x 400 mg tablets) orally once daily (OD) continuously. Pazopanib was to be taken at least one hour before or at least two hours after a meal. Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.

Reporting group title	Sunitinib 50 mg

Reporting group description:

Participants were administered sunitinib 50 mg orally once daily in 6-week cycles (4 weeks of treatment, followed by 2 weeks without treatment). Participants received study treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent for any other reasons.

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the interval between the date of randomization and the earliest date of progressive disease (PD), as defined by the Independent Review Committee (IRC), or death due to any cause. The IRC defined PD per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1. Per RECIST, PD is defined as a >=20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of >=1 new lesion.

End point type	Primary

End point timeframe:

From randomization until the earliest date of disease progression or date of death from any cause, assessed up to approximately 39 months

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	557	553		
Units: Months				
median (confidence interval 95%)	8.4 (8.3 to 10.9)	9.5 (8.3 to 11.1)		

Statistical analyses

Statistical analysis title	Progression-free Survival (PFS)
Comparison groups	Pazopanib 800 mg v Sunitinib 50 mg

Number of subjects included in analysis	1110
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.0466
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8982
upper limit	1.2195

Secondary: Overall Response Rate (ORR) as assessed by independent review

End point title	Overall Response Rate (ORR) as assessed by independent review

End point description:

The number of participants with evidence of Complete Response (CR) (the disappearance of all target and non-target lesions), Partial Response (PR) (at least a 30% decrease in the sum of the longest diameters [LD] of target lesions, taking as a reference the Baseline sum LD), Stable Disease (small changes that do not meet previously given criteria, taking as reference the smallest sum LD since the treatment started), or Progressive Disease (a >=20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started) was evaluated by an independent review per RECIST, Version 1.

End point type	Secondary

End point timeframe:

From randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 39 months

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	557	553		
Units: Participants				
Complete Response	1	3		
Partial Response	170	134		
Stable Disease	216	242		
Progressive Disease	97	105		
Unknown	73	69		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from randomization until death due to any cause.

End point type	Secondary

End point timeframe:

From randomization until date of death from any cause, assessed up to approximately 62 months

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	557	553		
Units: Months				
median (confidence interval 95%)	28.3 (26.0 to 35.5)	29.1 (25.4 to 33.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was defined as the time from the start of treatment until the first documented evidence of CR (the disappearance of all target and non-target lesions) or PR (at least a 30% decrease in the sum of the LD of target lesions, taking as a reference the Baseline sum LD), whichever comes first. CR and PR were evaluated by an independent review per RECIST, Version 1.

End point type	Secondary

End point timeframe:

From randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 39 months

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	137		
Units: Weeks				
median (confidence interval 95%)	11.9 (11.3 to 12.1)	17.4 (12.7 to 18.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale scores at Day 28 of Cycles 1-4

End point title	Change from Baseline in Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale scores at Day 28 of

	Cycles 1-4

End point description:

FACIT Fatigue Subscale is a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a four point Likert scale (4 = not at all fatigued to 0 = very much fatigued). The total score range is from 0-52. The higher the score, the lower the fatigue level.

End point type	Secondary

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	375		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=353,375)	-5.3 (± 11.00)	-6.7 (± 10.93)		
Week 10 (n=293,330)	-4.0 (± 10.28)	-6.3 (± 10.65)		
Week 16 (n=273,280)	-3.8 (± 10.13)	-6.9 (± 11.16)		
Week 22 (n=227,240)	-2.9 (± 9.77)	-6.5 (± 10.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Adverse Events

End point title	Number of participants with Adverse Events

End point description:

The distribution of adverse events was done via the analysis of frequencies for Adverse Event (AEs) and Serious Adverse Event (SAEs), through the monitoring of relevant clinical and laboratory safety parameters.

End point type	Secondary

End point timeframe:

From study treatment start date till 28 days safety follow-up, assessed up to approximately 152 months

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	548		
Units: Participants				
Adverse Events (AEs)	551	535		
Serious Adverse Events (SAEs)	242	227		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as the time from the first documented evidence of response (CR or PR) until the first documented sign of disease progression (a >=20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of >=1 new lesion) or death, if sooner. CR=the disappearance of all target and non-target lesions. PR=at least a 30% decrease in the sum of the LD of target lesions, taking as a reference the Baseline sum LD.

End point type	Secondary

End point timeframe:

From the date of the first documented response (CR or PR) to the date of first documented progression or death due to any cause, assessed up to approximately 39 months

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	137		
Units: Months				
median (confidence interval 95%)	13.8 (12.2 to 16.4)	18.0 (14.3 to 22.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale disease-related symptoms-physical (DRS-P) domain score at Day 28 of Cycles 1-4

End point title	Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale disease-related symptoms-physical (DRS-P) domain score at Day 28 of Cycles 1-4

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 (Disease-Related Symptoms – Physical (FKSI-DRS-P), Disease-Related Symptoms – Emotional (FKSI-DRS-E), Treatment Side-Effects (FKSI-TSE), Function/Well-Being (FKSI-FWB)) experienced in the past 7 days. Participants are asked to respond to a total of 19 questions regarding symptoms, side effects, and well being 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 score of 0 to 76). A negative mean indicates a worsening of condition.

End point type	Secondary

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	378		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=358,378)	-2.9 (± 6.39)	-3.9 (± 6.87)		
Week 10 (n=296,336)	-2.3 (± 6.69)	-3.2 (± 6.76)		
Week 16 (n=269,283)	-2.6 (± 6.70)	-3.2 (± 6.61)		
Week 22 (n=224,238)	-1.3 (± 6.29)	-2.7 (± 6.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale disease related symptoms-emotional (DRS-E) domain score at Day 28 of Cycles 1-4

End point title	Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale disease related symptoms-emotional (DRS-E) domain score at Day 28 of Cycles 1-4

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 (Disease-Related Symptoms – Physical (FKSI-DRS-P), Disease-Related Symptoms – Emotional (FKSI-DRS-E), Treatment Side-Effects (FKSI-TSE), Function/Well-Being (FKSI-FWB)) experienced in the past 7 days. Participants are asked to respond to a total of 19 questions regarding symptoms, side effects, and well being 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 score of 0 to 76). A negative mean indicates a worsening of condition.

End point type	Secondary

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	367		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=344,367)	0.3 (± 1.31)	0.4 (± 1.22)		
Week 10 (n=287,329)	0.4 (± 1.33)	0.5 (± 1.32)		
Week 16 (n=260,277)	0.5 (± 1.39)	0.6 (± 1.30)		
Week 22 (n=220,233)	0.6 (± 1.27)	0.6 (± 1.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale treatment side effects (TSE) domain score at Day 28 of Cycles 1-4

End point title	Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale treatment side effects (TSE) domain score at Day 28 of Cycles 1-4

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 (Disease-Related Symptoms – Physical (FKSI-DRS-P), Disease-Related Symptoms – Emotional (FKSI-DRS-E), Treatment Side-Effects (FKSI-TSE), Function/Well-Being (FKSI-FWB)) experienced in the past 7 days. Participants are asked to respond to a total of 19 questions regarding symptoms, side effects, and well being 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 score of 0 to 76). A negative mean indicates a worsening of condition.

End point type	Secondary

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	350		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=326,350)	-1.5 (± 2.45)	-2.0 (± 2.35)		
Week 10 (n=267,305)	-1.9 (± 2.66)	-2.4 (± 2.62)		
Week 16 (n=244,254)	-2.1 (± 2.79)	-2.8 (± 2.46)		
Week 22 (n=201,218)	-2.4 (± 2.75)	-2.4 (± 2.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale functional well being (FWB) domain score at Day 28 of Cycles 1-4

End point title	Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale functional well being (FWB) domain score at Day 28 of Cycles 1-4

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 (Disease-Related Symptoms – Physical (FKSI-DRS-P), Disease-Related Symptoms – Emotional (FKSI-DRS-E), Treatment Side-Effects (FKSI-TSE), Function/Well-Being (FKSI-FWB)) experienced in the past 7 days. Participants are asked to respond to a total of 19 questions regarding symptoms, side effects, and well being 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 score of 0 to 76). A negative mean indicates a worsening of condition.

End point type	Secondary

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	357	378		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=357,378)	-1.0 (± 4.01)	-1.3 (± 3.63)		
Week 10 (n=298,331)	-0.6 (± 4.00)	-1.1 (± 3.94)		
Week 16 (n=267,278)	-0.8 (± 4.08)	-1.0 (± 3.96)		
Week 22 (n=228,234)	-0.7 (± 3.93)	-1.0 (± 3.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale total score at Day 28 of Cycles 1-4

End point title	Change from Baseline in the FACT-Kidney Symptom Index-19 (FKSI-19) scale total score at Day 28 of Cycles 1-4

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 (Disease-Related Symptoms – Physical (FKSI-DRS-P), Disease-Related Symptoms – Emotional (FKSI-DRS-E), Treatment Side-Effects (FKSI-TSE), Function/Well-Being (FKSI-FWB)) experienced in the past 7 days. Participants are asked to respond to a total of 19 questions regarding symptoms, side effects, and well being 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 score of 0 to 76). A negative mean indicates a worsening of condition.

End point type	Secondary

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	379		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=358,379)	-5.0 (± 10.82)	-6.6 (± 10.55)		
Week 10 (n=296,337)	-4.2 (± 10.95)	-6.3 (± 11.21)		
Week 16 (n=267,284)	-4.8 (± 11.13)	-6.3 (± 10.67)		
Week 22 (n=225,238)	-3.7 (± 10.49)	-5.5 (± 10.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Supplementary Quality of Life Questions (SQLQ) scale worst soreness scores at Day 28 of Cycles 1-4

End point title	Change from Baseline in the Supplementary Quality of Life Questions (SQLQ) scale worst soreness scores at Day 28 of Cycles 1-4

End point description:

The SQLQ scale consists of 5 items that assess the worst mouth and throat, hand, and foot soreness, as well as limitations due to mouth/throat and foot soreness. Participants were asked to assess their worst mouth/throat, hand, and foot soreness by answering the question of " In the past 4 weeks, what was your worst mouth/throat, hand, and foot soreness?" by using the following 4-point scale: 0, I never had any soreness; 1, I had a little bit of soreness; 2, I had quite a lot of soreness; 3, I had severe soreness. A positive mean change from Baseline represents a worsening of condition.

End point type	Secondary

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	184		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Mouth and Throat Soreness, Week 4 (n=202,180)	0.4 (± 0.87)	1.0 (± 0.99)		
Mouth and Throat Soreness, Week 10 (n=164,155)	0.4 (± 0.88)	0.9 (± 0.99)		
Mouth and Throat Soreness, Week 16 (n=137,138)	0.3 (± 0.73)	0.8 (± 0.89)		
Mouth and Throat Soreness, Week 22 (n=120,117)	0.2 (± 0.75)	0.8 (± 0.81)		
Hand Soreness, Week 4 (n=200,184)	0.2 (± 0.71)	0.3 (± 0.72)		
Hand Soreness, Week 10 (n=164,153)	0.3 (± 0.84)	0.7 (± 0.85)		
Hand Soreness, Week 16 (n=139,136)	0.4 (± 0.76)	0.6 (± 0.80)		
Hand Soreness, Week 22 (n=123,115)	0.3 (± 0.69)	0.6 (± 0.82)		
Foot Soreness, Week 4 (n=199,182)	0.2 (± 0.86)	0.4 (± 0.80)		
Foot Soreness, Week 10 (n=163,153)	0.3 (± 1.00)	0.6 (± 0.99)		
Foot Soreness, Week 16 (n=140,136)	0.3 (± 1.07)	0.8 (± 0.99)		
Foot Soreness, Week 22 (n=123,116)	0.3 (± 1.04)	0.9 (± 0.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Supplementary Quality of Life Questions (SQLQ) limitations due to mouth and throat soreness score at Day 28 of Cycles 1-4

End point title	Change from Baseline in the Supplementary Quality of Life Questions (SQLQ) limitations due to mouth and throat soreness score at Day 28 of Cycles 1-4

End point description:

The SQLQ consists of 5 items assessing the worst mouth/throat, hand, and foot soreness, and limitations due to mouth/throat and foot soreness. Participants assessed the limitations caused by their mouth/throat soreness by answering the question of "In the past 4 weeks, how much did your worst mouth/throat soreness limit you in the following activities: swallowing/eating/drinking/talking/sleeping" by using the following 4-point scale: 0, not limited; 1, limited a little; 2, limited a lot; 3, unable to do. The overall limitation score (15=best; 0=worst), based on the individual scores for the 5 activities, is derived as follows: the actual scores were rescored by subtracting the actual score from "3" for each of the 5 categories. A high score indicates less limitation. Change from Baseline was calculated as the assessment week value minus the Baseline value. A negative mean change from Baseline represents a worsening of condition.

End point type	Secondary

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	170		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=177,170)	-0.9 (± 2.09)	-1.8 (± 2.91)		
Week 10 (n=144,137)	-0.9 (± 1.91)	-1.8 (± 3.06)		
Week 16 (n=125,122)	-0.6 (± 1.56)	-1.3 (± 2.30)		
Week 22 (n=111,107)	-0.4 (± 1.67)	-1.4 (± 1.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Supplementary Quality of Life Questions (SQLQ) Limitations Due to Foot Soreness Scores at Day 28 of Cycles 1-4

End point title	Change From Baseline in the Supplementary Quality of Life Questions (SQLQ) Limitations Due to Foot Soreness Scores at Day 28 of Cycles 1-4

End point description:

The SQLQ consists of 5 items assessing the worst mouth/throat, hand, and foot soreness, and limitations due to mouth/throat and foot soreness. Participants assessed the limitations caused by their foot soreness by answering the question of "In the past 4 weeks, how much did your worst foot soreness limit you in each of the following activities: standing/walking/climbing stairs/sleeping/ability to do usual activities" by using the following 4-point scale: 0, not limited; 1, limited a little; 2, limited a lot; 3, unable to do. The overall limitation score (15=best; 0=worst), based on the individual scores for the 5 activities, is derived as follows: the actual scores were rescored by subtracting the actual score from "3" for each of the 5 categories. A high score indicates less limitation. Change from Baseline was

calculated as the assessment week value minus the Baseline value. A negative mean change from Baseline represents a worsening of condition.

End point type	Secondary

End point timeframe:

Baseline (predose), Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	163		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=170,163)	-0.6 (± 2.94)	-1.0 (± 2.94)		
Week 10 (n=133,136)	-1.1 (± 3.02)	-1.5 (± 3.76)		
Week 16 (n=114,126)	-1.2 (± 3.42)	-2.2 (± 3.50)		
Week 22 (n=105,108)	-1.3 (± 3.25)	-2.1 (± 3.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Analysis for the Cancer Treatment Satisfaction Questionnaire (CTSQ) Score at Day 28 of Cycles 1-4

End point title	Summary of Analysis for the Cancer Treatment Satisfaction Questionnaire (CTSQ) Score at Day 28 of Cycles 1-4

End point description:

The CTSQ assesses 3 domains related to the participant's satisfaction with cancer therapy: Expectations of Therapy (ET), Feelings about Side Effects (FSE), and Satisfaction with Therapy (SWT). Participants shared their thoughts on their cancer therapy (9 questions), their satisfaction with their most recently administered cancer therapy (6 questions), and if they would take the same cancer therapy if given the choice to do so again. All questions were assessed on a 5-point scale; 1, never; 5, always. Scores were averaged and transformed to a 0-100 scale; higher scores represent better treatment satisfaction.

End point type	Secondary

End point timeframe:

Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	383	386		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
ET, Week 4 (n=383,386)	71.7 (± 22.13)	71.3 (± 22.38)		
ET, Week 10 (n=321,346)	73.4 (± 21.62)	73.4 (± 19.37)		
ET, Week 16 (n=296,293)	73.9 (± 21.56)	72.9 (± 21.43)		
ET, Week 22 (n=250,250)	73.0 (± 21.40)	73.4 (± 20.43)		

FSE, Week 4 (n=340,360)	66.3 (± 24.00)	58.5 (± 23.59)		
FSE, Week 10 (n=298,323)	66.0 (± 23.09)	56.0 (± 22.23)		
FSE, Week 16 (n=274,277)	65.0 (± 23.01)	56.6 (± 22.02)		
FSE, Week 22 (n=235, 232)	67.1 (± 22.62)	57.8 (± 21.28)		
SWT, Week 4 (n=355,374)	80.9 (± 15.49)	79.0 (± 15.23)		
SWT, Week 10 (n=309,336)	84.5 (± 13.74)	80.4 (± 15.15)		
SWT, Week 16 (n=287,284)	85.3 (± 14.77)	80.5 (± 15.08)		
SWT, Week 22 (n=241,240)	85.4 (± 13.48)	81.4 (± 15.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of Non-study Medical Visits, Telephone Consultations, Hospital Days, and Emergency Room (ER) Visits Per 30 Days Through Week 24

End point title	Mean Number of Non-study Medical Visits, Telephone Consultations, Hospital Days, and Emergency Room (ER) Visits Per 30 Days Through Week 24

End point description:

Non-study medical visits were defined as the sum of primary care physician visits, nurse practitioner/physician's assistant/nurse visits, and medical or surgical specialist visits. Days hospitalized were defined as the sum of days in the general ward and days in intensive care. The number of telephone consultations and ER visits was assessed via individual questions on the electronic Case Report Form. The endpoint was totaled through Week 24, divided by the number of days on treatment for each participant, then multiplied by 30 days to get the number of visits per 30 days.

End point type	Secondary

End point timeframe:

From Day 1 up to Week 24

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	432		
Units: events per 30 days				
arithmetic mean (standard deviation)				
Non-Study Medical Visits	0.726 (± 1.472)	0.779 (± 1.690)		
Telephone Consultations	0.279 (± 0.718)	0.312 (± 0.656)		
Hospital Days	0.402 (± 2.273)	0.562 (± 2.187)		
ER Visits	0.037 (± 0.156)	0.067 (± 0.195)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of Laboratory Visits, Radiology Visits, Home Healthcare Visits, and Medical Procedures at Day 28 of Cycles 1-4

End point title	Mean Number of Laboratory Visits, Radiology Visits, Home Healthcare Visits, and Medical Procedures at Day 28 of Cycles 1-4

End point description:

The number of non-study laboratory visits (NSLVs), non-study radiology visits (NSRVs), and home healthcare visits (HHVs) were each collected as a single question on the eCRF. The number of non-study medical or surgical procedures (MSPs) was defined as the sum of procedures performed at outpatient or physician clinics, as well as those performed during any inpatient hospitalization.

End point type	Secondary

End point timeframe:

Day 28 of Cycles 1-4 (average of Weeks 4, 10, 16, and 22, respectively)

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	432		
Units: visits				
arithmetic mean (standard deviation)				
NSLV, Cycle 1 (n=417,414)	0.3 (± 1.25)	0.3 (± 1.14)		
NSLV, Cycle 2 (n=345,363)	0.3 (± 0.97)	0.4 (± 1.35)		
NSLV, Cycle 3 (n=299,304)	0.2 (± 0.67)	0.2 (± 0.58)		
NSLV, Cycle 4 (n=265,254)	0.1 (± 0.49)	0.1 (± 0.47)		
NSRV, Cycle 1 (n=419,414)	0.1 (± 0.44)	0.1 (± 0.56)		
NSRV, Cycle 2 (n=348,364)	0.1 (± 0.36)	0.1 (± 0.88)		
NSRV, Cycle 3 (n=299,305)	0.0 (± 0.28)	0.1 (± 0.33)		
NSRV, Cycle 4 (n=266,255)	0.0 (± 0.24)	0.1 (± 0.46)		
HHV, Cycle 1 (n=418,411)	0.0 (± 0.44)	0.1 (± 0.77)		
HHV, Cycle 2 (n=343,363)	0.1 (± 0.52)	0.1 (± 0.64)		
HHV, Cycle 3 (n=298,304)	0.1 (± 0.72)	0.0 (± 0.37)		
HHV, Cycle 4 (n=265,254)	0.0 (± 0.49)	0.1 (± 1.77)		
NSP, Cycle 1 (n=417,413)	0.2 (± 0.69)	0.3 (± 2.52)		
NSP, Cycle 2 (n=344,363)	0.2 (± 0.68)	0.2 (± 1.17)		
NSP, Cycle 3 (n=298,304)	0.2 (± 0.60)	0.3 (± 1.98)		
NSP, Cycle 4 (n=266,254)	0.2 (± 0.85)	0.3 (± 1.73)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: All collected deaths

End point title	All collected deaths

End point description:

Pre-treatment deaths were collected from day of participant’s informed consent to the day before first dose of study medication.
On-treatment deaths were collected from first dose of study medication to 28 days after last dose of study medication (on-treatment), up to approximately 129 months.
Deaths were collected in the post treatment survival follow up from 29 days after last dose of study

medication until the end of the study, up to approximately 152 months.

End point type	Other pre-specified

End point timeframe:

Pre-treatment deaths: Up to 21 days prior to treatment. On-treatment deaths: Up to 129 months. Post-treatment deaths: up to 152 months.

End point values	Pazopanib 800 mg	Sunitinib 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	557	553		
Units: Participants				
Pre-treatment deaths	0	0		
On-treatment deaths	25	22		
Post-treatment deaths	310	312		
All deaths	335	334		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from first dose of study medication until the last dose plus 28 days post-treat follow-up, assessed up to approximately 129 months.

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	24.1

Reporting groups

Reporting group title	Pazopanib

Reporting group description:

Pazopanib

Reporting group title	Total

Reporting group description:

Total

Reporting group title	Sunitinib

Reporting group description:

Sunitinib

Serious adverse events	Pazopanib	Total	Sunitinib
Total subjects affected by serious adverse events			
subjects affected / exposed	242 / 554 (43.68%)	469 / 1102 (42.56%)	227 / 548 (41.42%)
number of deaths (all causes)	335	669	334
number of deaths resulting from adverse events	3	11	8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioblastoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Gastric cancer			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Endometrial cancer metastatic			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholesteatoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Lung neoplasm malignant			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Adenocarcinoma of colon			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			

subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Metastases to central nervous system			
subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Metastases to liver			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Metastasis			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraneoplastic syndrome			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Parathyroid tumour benign			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Renal cancer metastatic			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Signet-ring cell carcinoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Tumour haemorrhage			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Tumour rupture			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial rupture			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Deep vein thrombosis			

subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry gangrene			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Giant cell arteritis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Haematoma			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	7 / 554 (1.26%)	13 / 1102 (1.18%)	6 / 548 (1.09%)
occurrences causally related to treatment / all	5 / 7	9 / 13	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	2 / 554 (0.36%)	3 / 1102 (0.27%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	2 / 2	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			

subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 554 (0.90%)	18 / 1102 (1.63%)	13 / 548 (2.37%)
occurrences causally related to treatment / all	3 / 5	10 / 18	7 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 554 (0.18%)	4 / 1102 (0.36%)	3 / 548 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Impaired healing			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	3 / 554 (0.54%)	15 / 1102 (1.36%)	12 / 548 (2.19%)
occurrences causally related to treatment / all	3 / 3	14 / 16	11 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Death			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Chest pain			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	2 / 554 (0.36%)	6 / 1102 (0.54%)	4 / 548 (0.73%)
occurrences causally related to treatment / all	2 / 2	3 / 6	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Penile oedema			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bartholin's cyst			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	3 / 554 (0.54%)	5 / 1102 (0.45%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	1 / 3	3 / 5	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 554 (0.00%)	6 / 1102 (0.54%)	6 / 548 (1.09%)
occurrences causally related to treatment / all	0 / 0	4 / 6	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	5 / 554 (0.90%)	13 / 1102 (1.18%)	8 / 548 (1.46%)
occurrences causally related to treatment / all	1 / 5	4 / 14	3 / 9
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

Laryngeal haemorrhage			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 554 (0.00%)	2 / 1102 (0.18%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	1 / 2	1 / 2
Acute respiratory failure			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Cough			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Lung infiltration			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Pleural effusion			
subjects affected / exposed	1 / 554 (0.18%)	12 / 1102 (1.09%)	11 / 548 (2.01%)
occurrences causally related to treatment / all	0 / 1	2 / 14	2 / 13
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Pleurisy			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 1	2 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	8 / 554 (1.44%)	15 / 1102 (1.36%)	7 / 548 (1.28%)
occurrences causally related to treatment / all	5 / 8	9 / 15	4 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary pain			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 554 (0.36%)	4 / 1102 (0.36%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 2	1 / 4	1 / 2
Pneumothorax			
subjects affected / exposed	2 / 554 (0.36%)	4 / 1102 (0.36%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Sleep disorder			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Mental status changes			

subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emotional distress			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Confusional state			
subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	35 / 554 (6.32%)	43 / 1102 (3.90%)	8 / 548 (1.46%)
occurrences causally related to treatment / all	36 / 37	42 / 45	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 554 (3.07%)	19 / 1102 (1.72%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	16 / 17	18 / 19	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	2 / 554 (0.36%)	4 / 1102 (0.36%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	2 / 2	3 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood calcium increased			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Blood creatine increased			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose decreased			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood magnesium decreased			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Blood potassium increased			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 554 (0.00%)	9 / 1102 (0.82%)	9 / 548 (1.64%)
occurrences causally related to treatment / all	0 / 0	8 / 9	8 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			

subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	7 / 554 (1.26%)	11 / 1102 (1.00%)	4 / 548 (0.73%)
occurrences causally related to treatment / all	6 / 7	10 / 11	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	6 / 554 (1.08%)	7 / 1102 (0.64%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	6 / 6	7 / 7	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 554 (0.54%)	3 / 1102 (0.27%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			

subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	2 / 2	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 554 (0.00%)	2 / 1102 (0.18%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Craniocerebral injury			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ilium fracture			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain herniation			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Ankle fracture			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Acetabulum fracture			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chemical poisoning			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Multiple fractures			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Patella fracture			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Tibia fracture			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			

subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 554 (0.18%)	5 / 1102 (0.45%)	4 / 548 (0.73%)
occurrences causally related to treatment / all	1 / 1	5 / 5	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Atrial thrombosis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Atrial fibrillation			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Acute myocardial infarction			

subjects affected / exposed	3 / 554 (0.54%)	5 / 1102 (0.45%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	2 / 3	3 / 5	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	3 / 554 (0.54%)	7 / 1102 (0.64%)	4 / 548 (0.73%)
occurrences causally related to treatment / all	2 / 3	6 / 7	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Torsade de pointes			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Central nervous system haemorrhage			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	2 / 554 (0.36%)	3 / 1102 (0.27%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	2 / 2	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic cerebral infarction			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	2 / 554 (0.36%)	3 / 1102 (0.27%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Cerebral small vessel ischaemic disease			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Cerebral ischaemia			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Cerebral infarction			
subjects affected / exposed	0 / 554 (0.00%)	2 / 1102 (0.18%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cerebral haemorrhage			
subjects affected / exposed	5 / 554 (0.90%)	6 / 1102 (0.54%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	3 / 5	4 / 6	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cerebellar haemorrhage			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Hemianaesthesia			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 554 (0.18%)	5 / 1102 (0.45%)	4 / 548 (0.73%)
occurrences causally related to treatment / all	1 / 1	3 / 5	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	4 / 554 (0.72%)	7 / 1102 (0.64%)	3 / 548 (0.55%)
occurrences causally related to treatment / all	0 / 4	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	2 / 554 (0.36%)	5 / 1102 (0.45%)	3 / 548 (0.55%)
occurrences causally related to treatment / all	1 / 2	1 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraplegia			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Motor dysfunction			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Lethargy			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	3 / 554 (0.54%)	4 / 1102 (0.36%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	2 / 3	3 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Immune thrombocytopenia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microangiopathic haemolytic anaemia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Lymphopenia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	9 / 554 (1.62%)	18 / 1102 (1.63%)	9 / 548 (1.64%)
occurrences causally related to treatment / all	6 / 9	13 / 18	7 / 9
deaths causally related to treatment / all	1 / 1	2 / 2	1 / 1
Febrile neutropenia			

subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	4 / 554 (0.72%)	28 / 1102 (2.54%)	24 / 548 (4.38%)
occurrences causally related to treatment / all	4 / 4	29 / 29	25 / 25
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polycythaemia			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 554 (0.36%)	9 / 1102 (0.82%)	7 / 548 (1.28%)
occurrences causally related to treatment / all	2 / 2	8 / 9	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 554 (0.00%)	2 / 1102 (0.18%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain			
subjects affected / exposed	3 / 554 (0.54%)	8 / 1102 (0.73%)	5 / 548 (0.91%)
occurrences causally related to treatment / all	1 / 3	4 / 8	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Abdominal pain upper			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal ulcer haemorrhage			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric fistula			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			

subjects affected / exposed	0 / 554 (0.00%)	2 / 1102 (0.18%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	3 / 554 (0.54%)	4 / 1102 (0.36%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	3 / 3	3 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	5 / 554 (0.90%)	15 / 1102 (1.36%)	10 / 548 (1.82%)
occurrences causally related to treatment / all	5 / 5	14 / 16	9 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 554 (0.36%)	4 / 1102 (0.36%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	1 / 2	2 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erosive oesophagitis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Gastritis			
subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	1 / 1	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	2 / 554 (0.36%)	4 / 1102 (0.36%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	1 / 2	1 / 2
Inguinal hernia			
subjects affected / exposed	2 / 554 (0.36%)	3 / 1102 (0.27%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	3 / 554 (0.54%)	3 / 1102 (0.27%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Haematochezia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 554 (0.00%)	2 / 1102 (0.18%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Glossodynia			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 554 (0.36%)	4 / 1102 (0.36%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 2	2 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			

subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	2 / 554 (0.36%)	3 / 1102 (0.27%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 2	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swollen tongue			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Pancreatitis acute			

subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	5 / 554 (0.90%)	7 / 1102 (0.64%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	5 / 6	7 / 8	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis ulcerative			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	6 / 554 (1.08%)	13 / 1102 (1.18%)	7 / 548 (1.28%)
occurrences causally related to treatment / all	5 / 6	11 / 13	6 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 554 (0.36%)	3 / 1102 (0.27%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 2	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	7 / 554 (1.26%)	15 / 1102 (1.36%)	8 / 548 (1.46%)
occurrences causally related to treatment / all	3 / 7	10 / 16	7 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice cholestatic			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 554 (0.00%)	2 / 1102 (0.18%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	8 / 554 (1.44%)	8 / 1102 (0.73%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	8 / 8	8 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Hepatic function abnormal			
subjects affected / exposed	7 / 554 (1.26%)	11 / 1102 (1.00%)	4 / 548 (0.73%)
occurrences causally related to treatment / all	7 / 7	11 / 11	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	1 / 1	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Cholelithiasis			
subjects affected / exposed	2 / 554 (0.36%)	3 / 1102 (0.27%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	2 / 554 (0.36%)	3 / 1102 (0.27%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder rupture			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	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	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Actinic keratosis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Decubitus ulcer			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureteric obstruction			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal impairment			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Renal haemorrhage			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 554 (0.18%)	5 / 1102 (0.45%)	4 / 548 (0.73%)
occurrences causally related to treatment / all	0 / 1	4 / 5	4 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Proteinuria			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	2 / 554 (0.36%)	5 / 1102 (0.45%)	3 / 548 (0.55%)
occurrences causally related to treatment / all	2 / 2	3 / 6	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	4 / 554 (0.72%)	13 / 1102 (1.18%)	9 / 548 (1.64%)
occurrences causally related to treatment / all	2 / 4	7 / 13	5 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	0 / 554 (0.00%)	2 / 1102 (0.18%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Muscular weakness			
subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 1	2 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc compression			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Haemarthrosis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	2 / 554 (0.36%)	3 / 1102 (0.27%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fistula			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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

Bone pain			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	3 / 554 (0.54%)	8 / 1102 (0.73%)	5 / 548 (0.91%)
occurrences causally related to treatment / all	0 / 3	0 / 8	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteolysis			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Bronchitis			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 554 (0.18%)	2 / 1102 (0.18%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complicated appendicitis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Gastroenteritis			
subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 1	2 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 554 (0.00%)	2 / 1102 (0.18%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perinephric abscess			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Peritonitis			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 554 (0.54%)	4 / 1102 (0.36%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 3	1 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Septic shock			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	3 / 554 (0.54%)	4 / 1102 (0.36%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	2 / 3	2 / 4	0 / 1
deaths causally related to treatment / all	1 / 1	1 / 2	0 / 1
Salmonella sepsis			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Retroperitoneal abscess			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal abscess			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Pyelonephritis			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Pneumonia			
subjects affected / exposed	7 / 554 (1.26%)	13 / 1102 (1.18%)	6 / 548 (1.09%)
occurrences causally related to treatment / all	1 / 7	2 / 14	1 / 7
deaths causally related to treatment / all	0 / 3	0 / 3	0 / 0
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 554 (0.36%)	4 / 1102 (0.36%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	2 / 2	3 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	2 / 554 (0.36%)	2 / 1102 (0.18%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	1 / 554 (0.18%)	3 / 1102 (0.27%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	0 / 1	3 / 6	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperlipasaemia			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Hypercalcaemia			
subjects affected / exposed	5 / 554 (0.90%)	6 / 1102 (0.54%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 5	0 / 9	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperamylasaemia			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 554 (0.18%)	1 / 1102 (0.09%)	0 / 548 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	8 / 554 (1.44%)	19 / 1102 (1.72%)	11 / 548 (2.01%)
occurrences causally related to treatment / all	4 / 8	15 / 21	11 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	2 / 554 (0.36%)	4 / 1102 (0.36%)	2 / 548 (0.36%)
occurrences causally related to treatment / all	1 / 2	2 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	4 / 554 (0.72%)	11 / 1102 (1.00%)	7 / 548 (1.28%)
occurrences causally related to treatment / all	1 / 4	6 / 11	5 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (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
Hypophosphataemia			

subjects affected / exposed	0 / 554 (0.00%)	1 / 1102 (0.09%)	1 / 548 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
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	Pazopanib	Total	Sunitinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	541 / 554 (97.65%)	1076 / 1102 (97.64%)	535 / 548 (97.63%)
Vascular disorders			
Hypertension			
subjects affected / exposed	256 / 554 (46.21%)	476 / 1102 (43.19%)	220 / 548 (40.15%)
occurrences (all)	314	605	291
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	47 / 554 (8.48%)	124 / 1102 (11.25%)	77 / 548 (14.05%)
occurrences (all)	58	165	107
Oedema peripheral			
subjects affected / exposed	58 / 554 (10.47%)	144 / 1102 (13.07%)	86 / 548 (15.69%)
occurrences (all)	71	194	123
Oedema			
subjects affected / exposed	15 / 554 (2.71%)	52 / 1102 (4.72%)	37 / 548 (6.75%)
occurrences (all)	16	61	45
Mucosal inflammation			
subjects affected / exposed	62 / 554 (11.19%)	203 / 1102 (18.42%)	141 / 548 (25.73%)
occurrences (all)	73	322	249
Fatigue			
subjects affected / exposed	305 / 554 (55.05%)	647 / 1102 (58.71%)	342 / 548 (62.41%)
occurrences (all)	392	1041	649
Face oedema			
subjects affected / exposed	12 / 554 (2.17%)	52 / 1102 (4.72%)	40 / 548 (7.30%)
occurrences (all)	12	79	67
Chills			

subjects affected / exposed	15 / 554 (2.71%)	58 / 1102 (5.26%)	43 / 548 (7.85%)
occurrences (all)	15	66	51
Asthenia			
subjects affected / exposed	47 / 554 (8.48%)	105 / 1102 (9.53%)	58 / 548 (10.58%)
occurrences (all)	91	195	104
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	86 / 554 (15.52%)	191 / 1102 (17.33%)	105 / 548 (19.16%)
occurrences (all)	113	241	128
Oropharyngeal pain			
subjects affected / exposed	39 / 554 (7.04%)	93 / 1102 (8.44%)	54 / 548 (9.85%)
occurrences (all)	41	108	67
Epistaxis			
subjects affected / exposed	49 / 554 (8.84%)	145 / 1102 (13.16%)	96 / 548 (17.52%)
occurrences (all)	65	220	155
Dyspnoea			
subjects affected / exposed	79 / 554 (14.26%)	171 / 1102 (15.52%)	92 / 548 (16.79%)
occurrences (all)	95	202	107
Dysphonia			
subjects affected / exposed	42 / 554 (7.58%)	54 / 1102 (4.90%)	12 / 548 (2.19%)
occurrences (all)	47	59	12
Psychiatric disorders			
Insomnia			
subjects affected / exposed	58 / 554 (10.47%)	119 / 1102 (10.80%)	61 / 548 (11.13%)
occurrences (all)	59	122	63
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	143 / 554 (25.81%)	236 / 1102 (21.42%)	93 / 548 (16.97%)
occurrences (all)	176	310	134
Amylase increased			
subjects affected / exposed	39 / 554 (7.04%)	63 / 1102 (5.72%)	24 / 548 (4.38%)
occurrences (all)	54	102	48
Aspartate aminotransferase increased			

subjects affected / exposed	128 / 554 (23.10%)	224 / 1102 (20.33%)	96 / 548 (17.52%)
occurrences (all)	164	338	174
Blood alkaline phosphatase increased			
subjects affected / exposed	40 / 554 (7.22%)	70 / 1102 (6.35%)	30 / 548 (5.47%)
occurrences (all)	41	87	46
Blood bilirubin increased			
subjects affected / exposed	51 / 554 (9.21%)	86 / 1102 (7.80%)	35 / 548 (6.39%)
occurrences (all)	82	153	71
Blood creatinine increased			
subjects affected / exposed	52 / 554 (9.39%)	137 / 1102 (12.43%)	85 / 548 (15.51%)
occurrences (all)	98	300	202
Blood lactate dehydrogenase increased			
subjects affected / exposed	40 / 554 (7.22%)	100 / 1102 (9.07%)	60 / 548 (10.95%)
occurrences (all)	64	243	179
Blood thyroid stimulating hormone increased			
subjects affected / exposed	33 / 554 (5.96%)	97 / 1102 (8.80%)	64 / 548 (11.68%)
occurrences (all)	45	162	117
Blood triglycerides increased			
subjects affected / exposed	21 / 554 (3.79%)	56 / 1102 (5.08%)	35 / 548 (6.39%)
occurrences (all)	42	103	61
Haemoglobin decreased			
subjects affected / exposed	34 / 554 (6.14%)	109 / 1102 (9.89%)	75 / 548 (13.69%)
occurrences (all)	47	237	190
Lipase increased			
subjects affected / exposed	43 / 554 (7.76%)	75 / 1102 (6.81%)	32 / 548 (5.84%)
occurrences (all)	66	119	53
Neutrophil count decreased			
subjects affected / exposed	23 / 554 (4.15%)	83 / 1102 (7.53%)	60 / 548 (10.95%)
occurrences (all)	48	192	144
Platelet count decreased			
subjects affected / exposed	36 / 554 (6.50%)	133 / 1102 (12.07%)	97 / 548 (17.70%)
occurrences (all)	68	330	262
Weight decreased			

subjects affected / exposed	86 / 554 (15.52%)	119 / 1102 (10.80%)	33 / 548 (6.02%)
occurrences (all)	99	134	35
White blood cell count decreased			
subjects affected / exposed	31 / 554 (5.60%)	105 / 1102 (9.53%)	74 / 548 (13.50%)
occurrences (all)	55	223	168
Nervous system disorders			
Taste disorder			
subjects affected / exposed	99 / 554 (17.87%)	244 / 1102 (22.14%)	145 / 548 (26.46%)
occurrences (all)	106	368	262
Headache			
subjects affected / exposed	124 / 554 (22.38%)	246 / 1102 (22.32%)	122 / 548 (22.26%)
occurrences (all)	159	338	179
Dysgeusia			
subjects affected / exposed	49 / 554 (8.84%)	107 / 1102 (9.71%)	58 / 548 (10.58%)
occurrences (all)	58	136	78
Dizziness			
subjects affected / exposed	71 / 554 (12.82%)	153 / 1102 (13.88%)	82 / 548 (14.96%)
occurrences (all)	87	192	105
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	51 / 554 (9.21%)	151 / 1102 (13.70%)	100 / 548 (18.25%)
occurrences (all)	114	364	250
Neutropenia			
subjects affected / exposed	60 / 554 (10.83%)	207 / 1102 (18.78%)	147 / 548 (26.82%)
occurrences (all)	121	504	383
Thrombocytopenia			
subjects affected / exposed	56 / 554 (10.11%)	236 / 1102 (21.42%)	180 / 548 (32.85%)
occurrences (all)	118	614	496
Anaemia			
subjects affected / exposed	36 / 554 (6.50%)	135 / 1102 (12.25%)	99 / 548 (18.07%)
occurrences (all)	49	209	160
Eye disorders			
Eyelid oedema			

subjects affected / exposed	18 / 554 (3.25%)	57 / 1102 (5.17%)	39 / 548 (7.12%)
occurrences (all)	32	124	92
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	24 / 554 (4.33%)	57 / 1102 (5.17%)	33 / 548 (6.02%)
occurrences (all)	32	70	38
Abdominal distension			
subjects affected / exposed	34 / 554 (6.14%)	61 / 1102 (5.54%)	27 / 548 (4.93%)
occurrences (all)	35	67	32
Abdominal pain			
subjects affected / exposed	72 / 554 (13.00%)	146 / 1102 (13.25%)	74 / 548 (13.50%)
occurrences (all)	86	194	108
Abdominal pain upper			
subjects affected / exposed	69 / 554 (12.45%)	118 / 1102 (10.71%)	49 / 548 (8.94%)
occurrences (all)	89	152	63
Constipation			
subjects affected / exposed	97 / 554 (17.51%)	230 / 1102 (20.87%)	133 / 548 (24.27%)
occurrences (all)	112	301	189
Diarrhoea			
subjects affected / exposed	349 / 554 (63.00%)	661 / 1102 (59.98%)	312 / 548 (56.93%)
occurrences (all)	752	1616	864
Dyspepsia			
subjects affected / exposed	78 / 554 (14.08%)	213 / 1102 (19.33%)	135 / 548 (24.64%)
occurrences (all)	93	302	209
Dry mouth			
subjects affected / exposed	26 / 554 (4.69%)	55 / 1102 (4.99%)	29 / 548 (5.29%)
occurrences (all)	29	61	32
Vomiting			
subjects affected / exposed	158 / 554 (28.52%)	306 / 1102 (27.77%)	148 / 548 (27.01%)
occurrences (all)	303	629	326
Stomatitis			
subjects affected / exposed	78 / 554 (14.08%)	232 / 1102 (21.05%)	154 / 548 (28.10%)
occurrences (all)	99	402	303
Oral pain			

subjects affected / exposed	12 / 554 (2.17%)	40 / 1102 (3.63%)	28 / 548 (5.11%)
occurrences (all)	14	58	44
Nausea			
subjects affected / exposed	248 / 554 (44.77%)	501 / 1102 (45.46%)	253 / 548 (46.17%)
occurrences (all)	399	879	480
Mouth ulceration			
subjects affected / exposed	22 / 554 (3.97%)	57 / 1102 (5.17%)	35 / 548 (6.39%)
occurrences (all)	28	80	52
Gastrooesophageal reflux disease			
subjects affected / exposed	19 / 554 (3.43%)	74 / 1102 (6.72%)	55 / 548 (10.04%)
occurrences (all)	19	88	69
Flatulence			
subjects affected / exposed	32 / 554 (5.78%)	47 / 1102 (4.26%)	15 / 548 (2.74%)
occurrences (all)	37	57	20
Skin and subcutaneous tissue disorders			
Yellow skin			
subjects affected / exposed	4 / 554 (0.72%)	97 / 1102 (8.80%)	93 / 548 (16.97%)
occurrences (all)	5	156	151
Pruritus			
subjects affected / exposed	23 / 554 (4.15%)	68 / 1102 (6.17%)	45 / 548 (8.21%)
occurrences (all)	29	86	57
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	163 / 554 (29.42%)	438 / 1102 (39.75%)	275 / 548 (50.18%)
occurrences (all)	248	863	615
Hair colour changes			
subjects affected / exposed	168 / 554 (30.32%)	222 / 1102 (20.15%)	54 / 548 (9.85%)
occurrences (all)	178	237	59
Dry skin			
subjects affected / exposed	44 / 554 (7.94%)	91 / 1102 (8.26%)	47 / 548 (8.58%)
occurrences (all)	53	106	53
Alopecia			
subjects affected / exposed	77 / 554 (13.90%)	122 / 1102 (11.07%)	45 / 548 (8.21%)
occurrences (all)	83	129	46
Rash			

subjects affected / exposed	95 / 554 (17.15%)	221 / 1102 (20.05%)	126 / 548 (22.99%)
occurrences (all)	143	344	201
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	99 / 554 (17.87%)	175 / 1102 (15.88%)	76 / 548 (13.87%)
occurrences (all)	148	301	153
Haematuria			
subjects affected / exposed	24 / 554 (4.33%)	52 / 1102 (4.72%)	28 / 548 (5.11%)
occurrences (all)	29	70	41
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	7 / 554 (1.26%)	36 / 1102 (3.27%)	29 / 548 (5.29%)
occurrences (all)	7	38	31
Hypothyroidism			
subjects affected / exposed	71 / 554 (12.82%)	209 / 1102 (18.97%)	138 / 548 (25.18%)
occurrences (all)	74	247	173
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	70 / 554 (12.64%)	163 / 1102 (14.79%)	93 / 548 (16.97%)
occurrences (all)	82	217	135
Myalgia			
subjects affected / exposed	34 / 554 (6.14%)	71 / 1102 (6.44%)	37 / 548 (6.75%)
occurrences (all)	39	83	44
Muscle spasms			
subjects affected / exposed	38 / 554 (6.86%)	61 / 1102 (5.54%)	23 / 548 (4.20%)
occurrences (all)	50	81	31
Arthralgia			
subjects affected / exposed	98 / 554 (17.69%)	180 / 1102 (16.33%)	82 / 548 (14.96%)
occurrences (all)	133	249	116
Back pain			
subjects affected / exposed	91 / 554 (16.43%)	180 / 1102 (16.33%)	89 / 548 (16.24%)
occurrences (all)	110	246	136
Flank pain			

subjects affected / exposed	14 / 554 (2.53%)	44 / 1102 (3.99%)	30 / 548 (5.47%)
occurrences (all)	18	58	40
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	46 / 554 (8.30%)	88 / 1102 (7.99%)	42 / 548 (7.66%)
occurrences (all)	77	142	65
Upper respiratory tract infection			
subjects affected / exposed	30 / 554 (5.42%)	64 / 1102 (5.81%)	34 / 548 (6.20%)
occurrences (all)	40	87	47
Urinary tract infection			
subjects affected / exposed	23 / 554 (4.15%)	52 / 1102 (4.72%)	29 / 548 (5.29%)
occurrences (all)	32	72	40
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	207 / 554 (37.36%)	410 / 1102 (37.21%)	203 / 548 (37.04%)
occurrences (all)	305	633	328
Hyperglycaemia			
subjects affected / exposed	16 / 554 (2.89%)	46 / 1102 (4.17%)	30 / 548 (5.47%)
occurrences (all)	24	64	40
Hyponatraemia			
subjects affected / exposed	22 / 554 (3.97%)	58 / 1102 (5.26%)	36 / 548 (6.57%)
occurrences (all)	34	86	52
Hypophosphataemia			
subjects affected / exposed	21 / 554 (3.79%)	53 / 1102 (4.81%)	32 / 548 (5.84%)
occurrences (all)	35	92	57

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2008	Amendment 1: Country Specific Amendment for Japan to add pharmacokinetic sampling for subjects randomized to pazopanib
01 April 2009	Amendment 2: Updates to Inclusion/Exclusion criteria, dose modification guidelines for liver toxicity, concomitant medication, addition of pharmacogenetic sampling and Supplementary Quality of Life Questions.
15 June 2009	Amendment 3: Country Specific Amendment for China to permit using 12.5 mg capsules of sunitinib for 50 mg, 37.5 mg, and 25 mg dose levels.
25 March 2011	Amendment 4: Change to safety visit schedule to decrease number of visits after Cycle 9 from Day 28 and Day 42 per cycle, to Day 42 per cycle. Changes in Data Analysis section to sample size assumptions and inclusion of subjects from Study A2201 for the analysis of safety and efficacy.
17 May 2013	Amendment 5: Changes to allow subjects continued access to pazopanib or sunitinib therapy following the Treatment Phase (in the absence of unacceptable toxicity, disease progression, or subject withdrawal). Subject treatment and disease management was conducted as indicated by local standard of medical care. Subjects who had already discontinued study treatment and were in progressive disease follow-up or survival follow-up were considered as having completed the study. Frequency of clinic visits reduced. Collection of safety information reduced to SAEs, pregnancies, AEs leading to study treatment discontinuation or other AEs the investigator deems important to report, and all other reasons leading to study treatment discontinuation.
05 December 2017	Amendment 6: Country specific amendment for China to permit use of pazopanib 200mg tablets (commercial supply) instead of 400mg tablets (clinical supply) in China.

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.

The full investigators lists and other Clinical Study Report appendices were not transferred over during the change in sponsorship from GlaxoSmithKline (GSK) to Novartis, the team could not confirm or quality control the investigator sites list.

Notes: