Clinical trial results:
A Phase III Study to Evaluate the Efficacy and Safety of Pazopanib Monotherapy Versus Placebo in Women Who Have Not Progressed after First Line Chemotherapy for Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Summary

EudraCT number	2008-004672-50
Trial protocol	IE DE AT FR ES DK BE IT SE
Global end of trial date	24 August 2017

Results information

Result version number	v1 (current)
This version publication date	07 September 2018
First version publication date	07 September 2018

Trial information

Trial identification

Sponsor protocol code	110655

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00866697
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 August 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine whether pazopanib (up to 24 months, at 800 mg daily) prolongs PFS compared to placebo in women with non-bulky, FIGO Stage II to IV epithelial ovarian, fallopian tube, or primary peritoneal cancer that had not progressed after first-line chemotherapy

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	26 May 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Australia: 65
Country: Number of subjects enrolled	Belgium: 38
Country: Number of subjects enrolled	China: 72
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	France: 178
Country: Number of subjects enrolled	Germany: 188
Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Italy: 91
Country: Number of subjects enrolled	Japan: 51
Country: Number of subjects enrolled	Korea, Republic of: 56
Country: Number of subjects enrolled	Norway: 11
Country: Number of subjects enrolled	Spain: 79
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	940
EEA total number of subjects	637

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)	725
From 65 to 84 years	214
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of a screening/baseline period, a treatment period and a posttreatment or follow-up period. Study treatment continued for 24 months unless subjects met any of the criteria for investigational product discontinuation, including withdrawal of consent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received matching placebo once daily for a maximum of 24 months.

Arm type	Placebo
Investigational medicinal product name	matching placebo for pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

tablet administered orally once daily for up to 24 months

Arm title	Pazopanib 800 mg

Arm description:

Participants received pazopanib 800 milligrams (mg) once daily for a maximum of 24 months.

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

Dosage and administration details:

800 mg tablet administered orally once daily for up to 24 months

Number of subjects in period 1	Placebo	Pazopanib 800 mg
Started	468	472
Completed	254	244
Not completed	214	228
Study closed/terminated	156	138
Physician decision	3	5
Consent withdrawn by subject	33	57
Lost to follow-up	22	28

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo once daily for a maximum of 24 months.	
Reporting group title	Pazopanib 800 mg
Reporting group description:	
Participants received pazopanib 800 milligrams (mg) once daily for a maximum of 24 months.	

Reporting group values	Placebo	Pazopanib 800 mg	Total
Number of subjects	468	472	940
Age categorical Units: Subjects			
Adults (18-64 years)	357	368	725
From 65-84 years	110	104	214
85 years and over	1	0	1
Age continuous Units: years			
median	57	56	
full range (min-max)	20 to 85	25 to 80	-
Sex: Female, Male Units: Subjects			
Female	468	472	940
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	1	2	3
American Indian or Alaska Native	1	1	2
Central/South Asian Heritage (Her)	1	0	1
Japanese/East Asian Her/South East Asian Her	102	106	208
White	363	363	726
AgeContinuous Units: Years			
arithmetic mean	56.8	55.8	
standard deviation	± 10.83	± 10.54	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo once daily for a maximum of 24 months.	
Reporting group title	Pazopanib 800 mg
Reporting group description:	
Participants received pazopanib 800 milligrams (mg) once daily for a maximum of 24 months.	

Primary: Investigator-assessed Progression-free Survival (PFS)

End point title	Investigator-assessed Progression-free Survival (PFS)
End point description:	
PFS is the interval between the date of randomization and the date of progression, defined by Response Evaluation Criteria in Solid Tumors (RECIST), or death due to any cause. Per RECIST, for target lesions (TLs), disease progression (PD) is defined as >=20% increase in the sum of the longest diameters (LD) of TLs, taking as a reference, the smallest sum LD recorded since the treatment started or the appearance of >=1 new lesions. For non-target lesions (NTLs), PD is defined as the appearance of >=1 new lesions and/or unequivocal progression of existing NTLs. Participants (par.) who did not progress/die were censored at the date of last adequate assessment (LAA). Par. who started a new anti-cancer therapy (ACT) prior to radiological progression/death were censored at the date of LAA prior to the new ACT. Par. who progressed/died after an extended period (>=12 months) without adequate assessment (AA) were censored at the date of their last visit with AA prior to progression/death.	
End point type	Primary
End point timeframe:	
From the date of randomization until the date of progression or death due to any cause (median time of follow-up was 17.9 months for pazopanib and 12.3 months for placebo)	

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	468	472		
Units: months				
median (confidence interval 95%)	12.3 (11.8 to 17.7)	17.9 (15.9 to 21.8)		

Statistical analyses

Statistical analysis title	PFS
Comparison groups	Placebo v Pazopanib 800 mg
Number of subjects included in analysis	940
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0021 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.766

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.643
upper limit	0.911

Notes:

[1] - The P-value from the stratified log-rank test was adjusted for the two stratification factors.

Secondary: Overall Survival - Median

End point title	Overall Survival - Median

End point description:

Overall surival is defined as the interval between the date of randomization and the date of death due to any cause. For participants who did not die, the time to death was censored at the time of last contact.

End point type	Secondary

End point timeframe:

From the date of randomization until the date of death due to any cause up to approximately 95 months

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	468	472		
Units: months				
median (confidence interval 95%)	64.0 (56.0 to 75.7)	59.1 (53.5 to 71.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival per Gynecologic Cancer Intergroup (GCIG) Criteria

End point title	Progression-free Survival per Gynecologic Cancer Intergroup (GCIG) Criteria

End point description:

Progression-free survival by GCIG criteria is defined as the time from the date of randomization to the earliest date of disease progression per GCIG criteria or death due to any cause. Progression is defined according to RECIST but can also be based upon serum CA-125. Progression or recurrence based on serum CA-125 levels are defined on the basis of a progressive serial elevation of serum CA-125, according to the following criteria: (1) participants (par.) with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 >=2x the upper normal limit (UNL) on two occasions at least one week apart or; (2) par. with elevated CA-125 pretreatment, which never normalizes, must show evidence of CA-125 >=2x the nadir value on two occasions at least one week apart or; (3) par. with CA-125 in the normal range pretreatment must show evidence of CA-125 >=2x the UNL on two occasions at least one week apart.

End point type	Secondary

End point timeframe:

From the date of randomization until the date of progression per GCIG criteria or death due to any cause (median time of follow-up was 16.8 months for pazopanib and 11.9 months for placebo)

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	468	472		
Units: months				
median (confidence interval 95%)	11.9 (10.6 to 14.9)	16.8 (12.6 to 18.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: 3-year Progression-free Survival

End point title	3-year Progression-free Survival

End point description:

3-year progression-free survival is defined as the percentage of participants who are progression-free at 3 years from randomization. Progression-free survival is defined as the time from the date of randomization to the earliest date of disease progression (defined by RECIST) or death due to any cause. Per RECIST, for target lesions, disease progression (PD) is defined as at least a 20% increase in the sum of the longest diameters (LD) of target lesions, taking as a reference, the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. For non-target lesions, PD is defined as the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. No analysis was done.

End point type	Secondary

End point timeframe:

Up to 3 years after randomization

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	468	472		
Units: percentage of participants	99	99		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 global health status score on Day 1 of Week 13 and Months 7, 10, 13, 16, and 25

End point title	Change from Baseline in the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 global health status score on Day 1 of Week 13 and Months 7, 10, 13, 16, and 25

End point description:

The EORTC QLQ-C30 is a self-reported, 30-item cancer-specific instrument that assesses 15 domains: 5 functional scales (physical, role, emotional, cognitive, and social functioning), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health status, or quality of life. Global health status is assessed using a 7-item Likert scale, ranging from 1 to 7 ("poor" to "excellent"). Participants were asked to respond to the following questions using the 7-item Likert scale: "How would you rate your overall health during the past week"; "How would you rate your overall quality of life during the past week?" Data are transformed to a scale ranging from 0 to 100. Higher scores represent better functioning (better quality of life). Mean changes from Baseline were calculated via mixed model-repeated measures analysis of covariance (ANCOVA).

End point type	Secondary

End point timeframe:

Baseline; Week 13; Months 7, 10, 13, 16, and 25

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	293		
Units: scores on a scale				
least squares mean (standard error)				
Week 13, n=393, 293|	0.58 (± 0.821)	-3.82 (± 0.950)		
Month 7, n=316, 223|	0.95 (± 0.962)	-4.65 (± 1.139)		
Month 10, n=240, 184|	1.98 (± 0.972)	-4.28 (± 1.115)		
Month 13, n=190, 140|	0.65 (± 1.200)	-1.80 (± 1.398)		
Month 16, n=137, 87|	1.39 (± 1.370)	0.96 (± 1.702)		
Month 25, n=92, 53|	3.86 (± 1.488)	-1.68 (± 1.934)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in QLQ-OV-28 module attitude to disease/treatment functional score on Day 1 of Week 13 and Months 7, 10, 13, 16, and 25

End point title	Change from Baseline in QLQ-OV-28 module attitude to disease/treatment functional score on Day 1 of Week 13 and Months 7, 10, 13, 16, and 25

End point description:

The OV (ovarian)-28 module is a 28-item addition to the EORTC QLQ-C30 that focuses on issues specific to ovarian cancer. It assesses attitude to disease/treatment functional symptoms, among others. Participants were asked to indicate the extent to which they experienced attention to disease/treatment functional problems in the week prior to assessment. Participants responded on a scale of 1-4 (1=not at all, 2=a little, 3=quite a bit, 4=very much) to the following questions: How much has your disease been a burden to you?; How much has your treatment been a burden to you?; Were you worried about your future health? Data are transformed to a scale ranging from 0 to 100. Higher scores represent better functioning (better quality of life). Mean changes from Baseline were calculated via mixed model-repeated measures ANCOVA.

End point type	Secondary

End point timeframe:

Baseline; Week 13; Months 7, 10, 13, 16, and 25

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	378	291		
Units: scores on a scale				
least squares mean (standard error)				
Week 13, n=378, 291|	9.92 (± 1.110)	4.24 (± 1.263)		
Month 7, n=299, 223|	12.10 (± 1.203)	4.94 (± 1.385)		
Month 10, n=228, 185|	14.31 (± 1.310)	8.54 (± 1.467)		
Month 13, n=182, 138|	15.45 (± 1.388)	10.07 (± 1.589)		
Month 16, n=133, 88|	15.81 (± 1.668)	13.25 (± 2.013)		
Month 25, n=90, 54|	16.50 (± 2.021)	5.72 (± 2.565)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in QLQ-OV-28 module body image functional score on Day 1 of Week 13 and Months 7, 10, 13, 16, and 25

End point title	Change from Baseline in QLQ-OV-28 module body image functional score on Day 1 of Week 13 and Months 7, 10, 13, 16, and 25

End point description:

The OV-28 module is a 28-item addition to the EORTC QLQ-C30 that focuses on issues specific to ovarian cancer. It assesses body image symptoms, among others. Participants were asked to indicate the extent to which they experienced body image problems in the week prior to assessment. Participants responded on a scale of 1-4 (1=not at all, 2=a little, 3=quite a bit, 4=very much) to the following questions: Have you felt physically less attractive as a result of your disease or treatment?; Have you been dissatisfied with your body? Data are transformed to a scale ranging from 0 to 100. Higher scores represent better functioning (better quality of life). Mean changes from Baseline were calculated via mixed model-repeated measures ANCOVA.

End point type	Secondary

End point timeframe:

Baseline; Week 13; Months 7, 10, 13, 16, and 25

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	386	297		
Units: scores on a scale				
least squares mean (standard error)				
Week 13, n=386, 297|	7.18 (± 1.063)	2.99 (± 1.210)		
Month 7, n=312, 230|	7.88 (± 1.141)	4.26 (± 1.319)		
Month 10, n=236, 190|	8.12 (± 1.319)	4.65 (± 1.482)		
Month 13, n=187, 145|	8.54 (± 1.421)	4.34 (± 1.616)		
Month 16, n=133, 91|	7.68 (± 1.633)	6.21 (± 1.941)		
Month 25, n=88, 56|	10.81 (± 1.856)	3.10 (± 2.281)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in QLQ-OV-28 module peripheral neuropathy (PN) symptoms score at Week 13 and Months 7, 10, 13, 16, and 25

End point title	Change from Baseline in QLQ-OV-28 module peripheral neuropathy (PN) symptoms score at Week 13 and Months 7, 10, 13, 16, and 25

End point description:

The OV-28 module is a 28-item addition to the EORTC QLQ-C30 that focuses on issues specific to ovarian cancer. It assesses peripheral neuropathy symptoms, among others. Participants were asked to indicate the extent to which they experienced peripheral neuropathy symptoms or problems in the week prior to assessment. Participants responded on a scale of 1-4 (1=not at all, 2=a little, 3=quite a bit, 4=very much) to the following questions: Did you have tingling hands or feet?; Have you had numbness in your fingers or toes?; Have you felt weak in your arms or legs? Data are transformed to a scale from 0 to 100. Lower scores represent better health (fewer symptoms) for symptom scales. Mean changes from Baseline were calculated via mixed model-repeated measures ANCOVA.

End point type	Secondary

End point timeframe:

Baseline; Week 13; Months 7, 10, 13, 16, and 25

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	297		
Units: scores on a scale				
least squares mean (standard error)				
Week 13, n=388, 297|	-3.34 (± 1.038)	-5.22 (± 1.184)		
Month 7, n=301, 226|	-6.12 (± 1.104)	-5.20 (± 1.270)		
Month 10, n=235, 188|	-7.85 (± 1.209)	-5.11 (± 1.361)		
Month 13, n=188, 140|	-8.76 (± 1.301)	-6.37 (± 1.499)		
Month 16, n=133, 90|	-8.66 (± 1.456)	-8.65 (± 1.745)		

Month 25, n=91, 55|	-9.47 (± 1.595)	-8.30 (± 2.010)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in QLQ-OV-28 module abdominal (AB)/gastrointestinal (GI) symptoms score at Week 13 and Months 7, 10, 13, 16,

End point title	Change from Baseline in QLQ-OV-28 module abdominal (AB)/gastrointestinal (GI) symptoms score at Week 13 and Months 7, 10, 13, 16, and 25

End point description:

The OV-28 module is a 28-item addition to the EORTC QLQ-C30 that focuses on issues specific to ovarian cancer. It assesses AB/GI symptoms, among others. Participants were asked to indicate the extent to which they experienced AB/GI symptoms or problems in the week prior to assessment. Participants responded on a scale of 1-4 (1=not at all, 2=a little, 3=quite a bit, 4=very much) to the following questions: Did you have abdominal pain?; Did you have a bloated feeling in your abdomen/stomach?; Did you have problems with your clothes feeling too tight?; Did you experience any change in bowel habit as a result of your disease or treatment?; Were you troubled by passing wind/gas/flatulence?; Have you felt full too quickly after beginning to eat?; Have you had indigestion/heartburn? Data are transformed to a scale from 0 to 100. Lower scores represent better health (fewer symptoms) for symptom scales. Mean changes from Baseline were calculated via mixed model-repeated measures ANCOVA.

End point type	Secondary

End point timeframe:

Baseline; Week 13; Months 7, 10, 13, 16, and 25

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	289		
Units: scores on a scale				
least squares mean (standard error)				
Week 13, n=388, 289|	0.93 (± 0.673)	6.62 (± 0.777)		
Month 7, n=308, 225|	2.36 (± 0.831)	11.11 (± 0.967)		
Month 10, n=232, 187|	2.74 (± 0.957)	11.33 (± 1.080)		
Month 13, n=187, 141|	3.64 (± 1.027)	12.29 (± 1.181)		
Month 16, n=133, 88|	3.69 (± 1.251)	8.11 (± 1.503)		
Month 25, n=91, 54|	3.82 (± 1.388)	11.86 (± 1.762)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in QLQ-OV-28 module hormonal/menopausal symptoms score at Week 13 and Months 7, 10, 13, 16, and 25

End point title	Change from Baseline in QLQ-OV-28 module hormonal/menopausal symptoms score at Week 13 and Months 7, 10, 13, 16, and 25

End point description:

The OV-28 module is a 28-item addition to the EORTC QLQ-C30 that focuses on issues specific to ovarian cancer. It assesses hormonal/menopausal symptoms, among others. Participants were asked to indicate the extent to which they experienced hormonal/menopausal symptoms or problems in the week prior to assessment. Participants responded on a scale of 1-4 (1=not at all, 2=a little, 3=quite a bit, 4=very much) to the following questions: Did you have hot flashes?; Did you have night sweats? Data are transformed to a scale from 0 to 100. Lower scores represent better health (fewer symptoms) for symptom scales. Mean changes from Baseline were calculated via mixed model-repeated measures ANCOVA.

End point type	Secondary

End point timeframe:

Baseline; Week 13; Months 7, 10, 13, 16, and 25

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	299		
Units: scores on a scale				
least squares mean (standard error)				
Week 13, n=398, 299|	-0.86 (± 1.026)	-0.95 (± 1.177)		
Month 7, n=315, 232|	-0.38 (± 1.185)	1.29 (± 1.371)		
Month 10, n=239, 189|	-2.17 (± 1.299)	0.83 (± 1.470)		
Month 13, n=186, 144|	-2.77 (± 1.396)	-0.74 (± 1.594)		
Month 16, n=136, 91|	-0.41 (± 1.610)	1.09 (± 1.920)		
Month 25, n=92, 55|	-1.58 (± 1.798)	-0.68 (± 2.280)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in QLQ-OV-28 module sexuality functional on Day 1 of Week 13 and Months 7, 10, 13, 16, and 25

End point title	Change from Baseline in QLQ-OV-28 module sexuality functional on Day 1 of Week 13 and Months 7, 10, 13, 16, and 25

End point description:

The OV-28 module is a 28-item addition to the EORTC QLQ-C30 that focuses on issues specific to ovarian cancer. It assesses sexual functioning symptoms, among others. Participants were asked to indicate the extent to which they experienced sexual functioning problems in the week prior to

assessment. Participants responded on a scale of 1-4 (1=not at all, 2=a little, 3=quite a bit, 4=very much) to the following questions: To what extent were you interested in sex?; To what extent were you sexually active?; If sexually active, to what extent was sex enjoyable for you?; If sexually active, did you have a dry vagina during sexual activity? Higher scores represent better functioning (better quality of life). Mean changes from Baseline were calculated via mixed model-repeated measures ANCOVA. Data were not analyzed due to low compliance (<50% at Baseline).

End point type	Secondary

End point timeframe:

Baseline; Week 13; Months 7, 10, 13, 16, and 25

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: scores on a scale				
least squares mean (standard error)	()	()		

Notes:

[2] - Data were not analyzed due to low compliance (<50% at Baseline).

[3] - Data were not analyzed due to low compliance (<50% at Baseline).

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in QLQ-OV-28 module other chemotherapy side effects (SE) symptoms score at Week 13 and Months 7, 10, 13, 16, and 25

End point title	Change from Baseline in QLQ-OV-28 module other chemotherapy side effects (SE) symptoms score at Week 13 and Months 7, 10, 13, 16, and 25

End point description:

The OV-28 module is a 28-item addition to the EORTC QLQ-C30 that focuses on issues specific to ovarian cancer. It assesses other chemotherapy SE symptoms, among others. Participants were asked to indicate the extent to which they experienced other chemotherapy SE symptoms/problems in the week prior to assessment. Participants responded on a scale of 1-4 (1=not at all, 2=a little, 3=quite a bit, 4=very much) to the following questions: Have you lost any hair?; If yes, were you upset by the loss of your hair?; Did food/drink taste different from usual?; Did you have aches or pains in your muscles or joints?; Did you have problems with hearing?; Did you urinate frequently?; Have you had skin problems (e.g., itchy, dry)? Data are transformed to a scale from 0 to 100. Lower scores represent better health (fewer symptoms) for symptom scales. Mean changes from Baseline were calculated via mixed model-repeated measures ANCOVA. Data were not analyzed due to low compliance (<50% at Baseline).

End point type	Secondary

End point timeframe:

Baseline; Week 13; Months 7, 10, 13, 16, and 25

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: scores on a scale				
least squares mean (standard error)	()	()		

Notes:

[4] - Data were not analyzed due to low compliance (<50% at Baseline).

[5] - Data were not analyzed due to low compliance (<50% at Baseline).

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EuroQOL EQ-5D (five dimensions) thermometer score at Week 13 and Months 7, 10, 13, 16, and 25

End point title	Change from Baseline in the EuroQOL EQ-5D (five dimensions) thermometer score at Week 13 and Months 7, 10, 13, 16, and 25

End point description:

The EuroQol (EQ-5D) questionnaire is a 2-page, generic, preference-based quality of life measure comprised of a 5-item health status measure and a visual analogue scale (VAS) and is used to generate two scores: the utility score and the thermometer score The thermometer score is based on a vertical VAS. The VAS is designed like a thermometer scale on which the best health state the participant can imagine is referenced at 100, and the worst health state the participant can imagine is marked by 0. Based on how good or bad the current health state is, the participant is asked to draw a line across the thermometer scale. For example, a line drawn across 46 on the scale of 0 to 100 would be coded 46. A negative adjusted mean change from Baseline represents a worsening of quality of life. Mean changes from Baseline were calculated via mixed model-repeated measures ANCOVA.

End point type	Secondary

End point timeframe:

Baseline; Week 13; Months 7, 10, 13, 16, and 25

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	288		
Units: scores on a scale				
least squares mean (standard error)				
Week 13, n=371, 288|	1.35 (± 0.876)	1.20 (± 0.993)		
Month 7, n=301, 220|	3.00 (± 0.929)	1.69 (± 1.076)		
Month 10, n=225, 179|	3.68 (± 1.048)	0.98 (± 1.179)		
Month 13, n=179, 136|	2.92 (± 1.194)	2.49 (± 1.369)		
Month 16, n=127, 87|	3.30 (± 1.219)	3.51 (± 1.451)		
Month 25, n=86, 53|	6.87 (± 1.534)	1.71 (± 1.937)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EQ-5D (five dimensions) utility score at Week 13 and Months 7, 10, 13, 16, and 25

End point title	Change from Baseline in the EQ-5D (five dimensions) utility

	score at Week 13 and Months 7, 10, 13, 16, and 25

End point description:

The EQ-5D utility score captures health status across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety and/or depression. Participants indicated the level of perceived problems in each of the five dimensions on three levels: 1, no problems; 2, some problems; 3, an extreme problem. Unique health states were defined by combining response levels from each of the five dimensions. For example, state 11111 indicates no problem on any of the five dimensions, whereas state 11223 indicates no problems with mobility or self-care; some problems with performing usual activities, moderate pain/discomfort; and extreme anxiety/depression. Responses are typically converted into health utilities or valuations on a scale ranging from 0 (worst health) to 1 (perfect health). A negative adjusted mean change from Baseline represents a worsening of quality of life. Mean changes from Baseline were calculated via mixed model-repeated measures ANCOVA.

End point type	Secondary

End point timeframe:

Baseline; Week 13; Months 7, 10, 13, 16, and 25

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	376	293		
Units: scores on a scale				
least squares mean (standard error)				
Week 13, n=376, 293|	0.00 (± 0.009)	-0.04 (± 0.010)		
Month 7, n=303, 226|	0.00 (± 0.010)	-0.04 (± 0.012)		
Month 10, n=228, 181|	0.01 (± 0.011)	-0.04 (± 0.012)		
Month 13, n=185, 138|	0.01 (± 0.011)	-0.01 (± 0.013)		
Month 16, n=129, 87|	-0.00 (± 0.014)	0.03 (± 0.017)		
Month 25, n=88, 56|	0.00 (± 0.016)	-0.02 (± 0.020)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated Grade 2, 3, and 4 on-therapy adverse events occurring in >=10% of participants in either treatment arm

End point title	Number of participants with the indicated Grade 2, 3, and 4 on-therapy adverse events occurring in >=10% of participants in either treatment arm

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs were graded according to the Common Terminiology Criteria for Adverse Events (CTCAE), Version 4.0. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life threatening; Grade 5, death. Each tx group had 1 subject who did not receive treatment. 5 subjects randomized to placebo received pazopanib. Total subjects in pazopanib=477

End point type	Secondary

End point timeframe:

From the date of the first dose of study drug to the date of the last dose plus 28 days (average of 9.8 months for pazopanib and 12.6 months for placebo)

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461[6]	472[7]		
Units: participants				
Hypertension, G2|	52	95		
Hypertension, G3|	25	139		
Hypertension, G4|	0	0		
Diarrhoea, G2|	22	97		
Diarrhoea, G3|	5	38		
Diarrhoea, G4|	0	1		
Nausea, G2|	15	42		
Nausea, G3|	0	4		
Nausea, G4|	0	0		
Headache, G2|	6	36		
Headache, G3|	3	8		
Headache, G4|	0	0		
Fatigue, G2|	19	42		
Fatigue, G3|	1	7		
Fatigue, G4|	0	0		
Neutropenia, G2|	17	51		
Neutropenia, G3|	2	29		
Neutropenia, G4|	2	3		
Dysgeusia, G2|	0	16		
Dysgeusia, G3|	0	0		
Dysgeusia, G4|	0	0		
Abdominal pain, G2|	21	26		
Abdominal pain, G3|	5	5		
Abdominal pain, G4|	0	0		
Alanine aminotransferase increased, G2|	4	22		
Alanine aminotransferase increased, G3|	0	24		
Alanine aminotransferase increased, G4|	1	4		
Hair color changes, G2|	0	13		
Hair color changes, G3|	0	0		
Hair color changes, G4|	0	0		
Decreased appetite, G2|	2	19		
Decreased appetite, G3|	0	1		
Decreased appetite, G4|	0	0		
Vomiting, G2|	8	21		
Vomiting, G3|	1	4		
Vomiting, G4|	0	0		
Aspartate aminotransferase increased, G2|	3	22		
Aspartate aminotransferase increased, G3|	0	10		

Aspartate aminotransferase increased, G4|	1	3		
Arthralgia, G2|	13	19		
Arthralgia, G3|	3	5		
Arthralgia, G4|	0	0		
Abdominal pain upper, G2|	3	20		
Abdominal pain upper, G3|	1	1		
Abdominal pain upper, G4|	0	1		
Asthenia, G2|	8	28		
Asthenia, G3|	0	6		
Asthenia, G4|	0	0		
Palmar-plantar erythrodysaesthesia syndrome, G2|	2	42		
Palmar-plantar erythrodysaesthesia syndrome, G3|	1	9		
Palmar-plantar erythrodysaesthesia syndrome, G4|	0	0		
Thrombocytopenia, G2|	1	15		
Thrombocytopenia, G3|	1	6		
Thrombocytopenia, G4|	2	3		
Hypothyroidism, G2|	9	19		
Hypothyroidism, G3|	0	0		
Hypothyroidism, G4|	0	0		
Constipation, G2|	20	12		
Constipation, G3|	1	1		
Constipation, G4|	0	0		

Notes:

[6] - Each tx group had 1 subject who did not receive treatment.

[7] - 1 sub=no tx. 5 subjects randomized to placebo received pazopanib. Total subject=477

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated on-therapy hematology grade shifts from Baseline grade

End point title	Number of participants with the indicated on-therapy hematology grade shifts from Baseline grade

End point description:

Hematology toxicities were graded according to the Common Terminiology Criteria for Adverse Events (CTCAE), Version 4.0. Grade refers to the severity of the toxicity. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each toxicity based on this general guideline: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life threatening; Grade 5, death. Participants with a missing Baseline grade were assumed to have a Baseline grade of 0. WBC=White blood cell.

End point type	Secondary

End point timeframe:

From the date of the first dose of study drug to the date of the last dose plus 28 days (average of 9.8 months for pazopanib and 12.6 months for placebo)

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	456	466		
Units: participants				
Hemoglobin, Any grade increase, n=456, 466|	44	68		
Hemoglobin, Increase to Grade 3, n=456, 466|	0	0		
Hemoglobin, Increase to Grade 4, n=456, 466|	0	0		
Lymphocytes, Any grade increase, n=453, 461|	75	91		
Lymphocytes, Increase to Grade 3, n=453, 461|	1	13		
Lymphocytes, Increase to Grade 4, n=453, 461|	0	0		
Neutrophils, Any grade increase, n=455, 462|	80	236		
Neutrophils, Increase to Grade 3, n=455, 462|	2	44		
Neutrophils, Increase to Grade 4, n=455, 462|	0	5		
Platelets, Any grade increase, n=456, 465|	25	167		
Platelets, Increase to Grade 3, n=456, 465|	1	8		
Platelets, Increase to Grade 4, n=456, 465|	1	4		
WBC count, Any grade increase, n=456, 465|	77	236		
WBC count, Increase to Grade 3, n=456, 465|	0	11		
WBC count, Increase to Grade 4, n=456, 465|	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated on-therapy chemistry grade shifts from Baseline grade

End point title	Number of participants with the indicated on-therapy chemistry grade shifts from Baseline grade

End point description:

Hematology toxicities were graded according to the Common Terminiology Criteria for Adverse Events (CTCAE), Version 4.0. Grade refers to the severity of the toxicity. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each toxicity based on this general guideline: Grade 1, mild; Grade 2, moderate; Grade 3, severe; Grade 4, life threatening; Grade 5, death. Participants with a missing Baseline grade were assumed to have a Baseline grade of 0.

End point type	Secondary

End point timeframe:

From the date of the first dose of study drug to the date of the last dose plus 28 days (average of 9.8 months for pazopanib and 12.6 months for placebo)

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	456	465		
Units: participants				
Albumin, Any grade increase, n=450, 455|	33	50		
Albumin, Increase to Grade 3, n=450, 455|	0	0		
Albumin, Increase to Grade 4, n=450, 455|	0	0		
Creatinine, Any grade increase, n=456, 465|	27	42		
Creatinine, Increase to Grade 3, n=456, 465|	0	1		
Creatinine, Increase to Grade 4, n=456, 465|	0	0		
Hypercalcemia, Any grade increase, n=456, 462|	33	16		
Hypercalcemia, Increase to Grade 3, n=456, 462|	0	0		
Hypercalcemia, Increase to Grade 4, n=456, 462|	0	0		
Hyperglycemia, Any grade increase, n=446, 453|	117	128		
Hyperglycemia, Increase to Grade 3, n=, 446, 453|	10	2		
Hyperglycemia, Increase to Grade 4, n=446, 453|	0	0		
Hyperkalemia, Any grade increase, n=455, 464|	39	38		
Hyperkalemia, Increase to Grade 3, n=455, 464|	2	1		
Hyperkalemia, Increase to Grade 4, n=455, 464|	0	2		
Hypermagnesemia, Any grade increase, n=439, 447|	11	20		
Hypermagnesemia, Increase to Grade 3, n=439, 447|	1	6		
Hypermagnesemia, Increase to Grade 4, n=439, 447|	1	0		
Hypernatremia, Any grade increase, n=455, 463|	26	25		
Hypernatremia, Increase to Grade 3, n=455, 463|	0	0		
Hypernatremia, Increase to Grade 4, n=455, 463|	0	0		
Hypocalcemia, Any grade increase, n=456, 462|	21	52		
Hypocalcemia, Increase to Grade 3, n=456, 462|	0	2		
Hypocalcemia, Increase to Grade 4, n=456, 462|	0	0		
Hypoglycemia, Any grade increase, n=446, 453|	25	41		
Hypoglycemia, Increase to Grade 3, n=446, 453|	2	0		

Hypoglycemia, Increase to Grade 4, n=446, 453|	2	2		
Hypokalemia, Any grade increase, n=455, 464|	31	40		
Hypokalemia, Increase to Grade 3, n=455, 464|	1	2		
Hypokalemia, Increase to Grade 4, n=455, 464|	1	0		
Hypomagnesemia, Any grade increase, n=439, 447|	55	65		
Hypomagnesemia, Increase to Grade 3, n=439, 447|	3	1		
Hypomagnesemia, Increase to Grade 4, n=439, 447|	0	2		
Hyponatremia, Any grade increase, n=455, 463|	37	45		
Hyponatremia, Increase to Grade 3, n=455, 463|	5	9		
Hyponatremia, Increase to Grade 4, n=455, 463|	0	0		
Phosphate, Any grade increase, n=409, 401|	33	24		
Phosphate, Increase to Grade 3, n=409, 401|	4	0		
Phosphate, Increase to Grade 4, n=409, 401|	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated treatment-emergent thyroid-stimulating hormone (TSH) elevations above 5 million units per liter (MU/L)

End point title	Number of participants with the indicated treatment-emergent thyroid-stimulating hormone (TSH) elevations above 5 million units per liter (MU/L)

End point description:

Participants were assessed for thyroid function abnormalities. Clinical hypothyroidism is defined as 5 <TSH <=10 MU/L and T4 <lower limit of normal (LLN).

End point type	Secondary

End point timeframe:

From the date of the first dose of study drug to the date of the last dose plus 28 days (average of 9.8 months for pazopanib and 12.6 months for placebo)

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	157		
Units: participants				
5 <TSH <=10 MU/L|	34	94		
10 <TSH <=20 MU/L|	4	36		
TSH >20 MU/L|	4	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - Hazard Ratio

End point title	Overall Survival - Hazard Ratio

End point description:

Overall surival is defined as the interval between the date of randomization and the date of death due to any cause. For participants who did not die, the time to death was censored at the time of last contact.

End point type	Secondary

End point timeframe:

From the date of randomization until the date of death due to any cause up to approximately 95 months

End point values	Placebo	Pazopanib 800 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	468	472		
Units: deaths				
deaths	253	241		
censored, follow up ended	215	231		

Statistical analyses

Statistical analysis title	hazard ratio
Comparison groups	Placebo v Pazopanib 800 mg
Number of subjects included in analysis	940
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6431
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.805
upper limit	1.145

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit up to approximately 95 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	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Pazopanib

Reporting group description:

Pazopanib

Serious adverse events	Placebo	Pazopanib	
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 461 (11.06%)	121 / 477 (25.37%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoma benign			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant lymphoma unclassifiable low grade			

subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of unknown primary site			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to abdominal cavity			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerated haemangioma			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 461 (0.00%)	8 / 477 (1.68%)	
occurrences causally related to treatment / all	0 / 0	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	0 / 461 (0.00%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrosis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 461 (0.22%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 461 (0.22%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ill-defined disorder			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			

subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 461 (0.43%)	9 / 477 (1.89%)	
occurrences causally related to treatment / all	1 / 3	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			

subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 461 (0.22%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 461 (0.00%)	18 / 477 (3.77%)	
occurrences causally related to treatment / all	0 / 0	19 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 461 (0.00%)	7 / 477 (1.47%)	
occurrences causally related to treatment / all	0 / 0	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ejection fraction decreased			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 461 (0.00%)	5 / 477 (1.05%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			

subjects affected / exposed	0 / 461 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			

subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cranial nerve disorder			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Presyncope			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transverse sinus thrombosis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 461 (0.22%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 461 (0.22%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous detachment			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous floaters			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal mass			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 461 (0.65%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain lower			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 461 (0.22%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 461 (0.22%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 461 (0.43%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocele			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			

subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	3 / 461 (0.65%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 461 (0.22%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 461 (0.22%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	3 / 461 (0.65%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 461 (0.43%)	4 / 477 (0.84%)	
occurrences causally related to treatment / all	0 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 461 (0.00%)	3 / 477 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			

subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 461 (0.43%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia intercostal			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 461 (0.22%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			

subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	1 / 461 (0.22%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 461 (0.00%)	2 / 477 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pyelonephritis			

subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 461 (0.65%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 461 (0.00%)	1 / 477 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 461 (0.22%)	0 / 477 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Pazopanib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	381 / 461 (82.65%)	462 / 477 (96.86%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	29 / 461 (6.29%)	23 / 477 (4.82%)	
occurrences (all)	30	24	
Hypertension			
subjects affected / exposed	87 / 461 (18.87%)	256 / 477 (53.67%)	
occurrences (all)	131	442	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	55 / 461 (11.93%)	66 / 477 (13.84%)	
occurrences (all)	62	78	
Fatigue			
subjects affected / exposed	66 / 461 (14.32%)	133 / 477 (27.88%)	
occurrences (all)	82	171	
Mucosal inflammation			
subjects affected / exposed	10 / 461 (2.17%)	32 / 477 (6.71%)	
occurrences (all)	10	43	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 461 (4.34%)	24 / 477 (5.03%)	
occurrences (all)	24	27	
Dyspnoea			
subjects affected / exposed	21 / 461 (4.56%)	31 / 477 (6.50%)	
occurrences (all)	21	34	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	27 / 461 (5.86%)	24 / 477 (5.03%)	
occurrences (all)	27	24	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	25 / 461 (5.42%)	73 / 477 (15.30%)	
occurrences (all)	33	86	
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 461 (5.21%)	66 / 477 (13.84%)	
occurrences (all)	29	76	
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 461 (0.65%)	24 / 477 (5.03%)	
occurrences (all)	3	26	
Blood bilirubin increased			
subjects affected / exposed	1 / 461 (0.22%)	29 / 477 (6.08%)	
occurrences (all)	1	36	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 461 (0.22%)	32 / 477 (6.71%)	
occurrences (all)	1	36	
Neutrophil count decreased			
subjects affected / exposed	11 / 461 (2.39%)	36 / 477 (7.55%)	
occurrences (all)	16	61	
Platelet count decreased			
subjects affected / exposed	1 / 461 (0.22%)	30 / 477 (6.29%)	
occurrences (all)	1	40	
Nervous system disorders			
Dizziness			
subjects affected / exposed	22 / 461 (4.77%)	26 / 477 (5.45%)	
occurrences (all)	24	27	
Dysgeusia			
subjects affected / exposed	13 / 461 (2.82%)	95 / 477 (19.92%)	
occurrences (all)	13	103	
Headache			
subjects affected / exposed	70 / 461 (15.18%)	135 / 477 (28.30%)	
occurrences (all)	130	211	
Blood and lymphatic system disorders			

Leukopenia			
subjects affected / exposed	5 / 461 (1.08%)	44 / 477 (9.22%)	
occurrences (all)	7	66	
Neutropenia			
subjects affected / exposed	23 / 461 (4.99%)	103 / 477 (21.59%)	
occurrences (all)	34	172	
Thrombocytopenia			
subjects affected / exposed	8 / 461 (1.74%)	48 / 477 (10.06%)	
occurrences (all)	8	60	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	94 / 461 (20.39%)	88 / 477 (18.45%)	
occurrences (all)	112	128	
Abdominal pain upper			
subjects affected / exposed	30 / 461 (6.51%)	67 / 477 (14.05%)	
occurrences (all)	49	78	
Constipation			
subjects affected / exposed	72 / 461 (15.62%)	38 / 477 (7.97%)	
occurrences (all)	94	43	
Diarrhoea			
subjects affected / exposed	79 / 461 (17.14%)	252 / 477 (52.83%)	
occurrences (all)	92	514	
Dyspepsia			
subjects affected / exposed	17 / 461 (3.69%)	24 / 477 (5.03%)	
occurrences (all)	18	25	
Nausea			
subjects affected / exposed	81 / 461 (17.57%)	174 / 477 (36.48%)	
occurrences (all)	100	222	
Stomatitis			
subjects affected / exposed	7 / 461 (1.52%)	27 / 477 (5.66%)	
occurrences (all)	10	33	
Vomiting			
subjects affected / exposed	39 / 461 (8.46%)	71 / 477 (14.88%)	
occurrences (all)	47	105	
Skin and subcutaneous tissue disorders			

Hair colour changes			
subjects affected / exposed	8 / 461 (1.74%)	95 / 477 (19.92%)	
occurrences (all)	8	98	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	7 / 461 (1.52%)	61 / 477 (12.79%)	
occurrences (all)	7	98	
Rash			
subjects affected / exposed	22 / 461 (4.77%)	42 / 477 (8.81%)	
occurrences (all)	26	55	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	8 / 461 (1.74%)	40 / 477 (8.39%)	
occurrences (all)	12	51	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	15 / 461 (3.25%)	49 / 477 (10.27%)	
occurrences (all)	15	53	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	68 / 461 (14.75%)	71 / 477 (14.88%)	
occurrences (all)	96	84	
Back pain			
subjects affected / exposed	38 / 461 (8.24%)	30 / 477 (6.29%)	
occurrences (all)	55	37	
Muscle spasms			
subjects affected / exposed	20 / 461 (4.34%)	35 / 477 (7.34%)	
occurrences (all)	23	44	
Myalgia			
subjects affected / exposed	34 / 461 (7.38%)	45 / 477 (9.43%)	
occurrences (all)	35	49	
Pain in extremity			
subjects affected / exposed	18 / 461 (3.90%)	38 / 477 (7.97%)	
occurrences (all)	21	41	
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	33 / 461 (7.16%)	32 / 477 (6.71%)	
occurrences (all)	46	44	
Viral upper respiratory tract infection			
subjects affected / exposed	24 / 461 (5.21%)	27 / 477 (5.66%)	
occurrences (all)	30	34	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 461 (3.25%)	79 / 477 (16.56%)	
occurrences (all)	19	87	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2009	- Provided additional tests for safety monitoring (ie, ECG and phosphorus); - expanded eligibility to ECOG 2 patients and added exclusion criterion regarding other (secondary) malignancies active within the last 5 years; - changed the trigger for more frequent CT/MRI scans; - changed requirement for separation by 24 hrs of the two blood pressure evaluations at Screening (exclusion criterion #6); - changed the grading of AEs from NCI CTCAE v3 to v4; - updated dose modification guidelines;
14 December 2009	France : -Added requirements that, whenever identified, abnormal levels of electrolytes (ie, calcium, magnesium, potassium) should be brought to normal for the subject to (continue to) be eligible for the study. - Added a requirement that potassium levels should be repeated at the start of IP administration if the last assessment was performed > 72 hours before treatment start. - Added changes in QTc from Baseline of >60msec as a criterion for interrupting the investigational product. - Added an Appendix listing medications known to be associated with prolongation of the QTc interval or TdP (to be used with caution). - Added an Appendix providing a corrective formula for calcium levels when albumin levels are low.
28 September 2010	-The treatment period was adjusted to 24 months throughout the document - Added additional (mainly safety) assessments at the previously-existing visits M16, M19, M25, and M31. - Statements added to explain that all patients should be considered for extension and outlining the algorithm for continued therapy.
23 July 2012	-Replaced the OS condition on the timing of the data cutoff for purposes of the primary analysis with a condition of completion of study treatment. - Re-spaced the OS interim analyses, to occur first, at the same time as the final PFS analysis, and second, when ~60% (ie, 330) of the required number of OS events (551) have been reported. - Eliminated unnecessary protocol requirements (eg, CT/MRI scans and CA-125 assessments) following the achievement of the data cut-off for the primary analysis.
09 May 2016	-Added a third OS interim analysis for futility at 80% information fraction (when approximately 441 OS events are reported. -Added additional OS follow-up for subjects whose last contact date is more than 6 months older at the time when 540 events are reported if the study continues after the third interim analysis or at the time when the decision is made to close the study after the third interim analysis.
16 June 2016	Deleted or replaced references to GSK or its staff with that of Novartis/Novartis and its authorized agents. Made administrative changes to align with Novartis processes and procedures.

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.

Study was closed following 3rd OS interim analysis as planned per protocol, which confirmed futility

Notes: