Clinical trial results:
Multicentre, randomised, double-blind Phase III trial to investigate the efficacy and safety of BIBF 1120 in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in patients with advanced ovarian cancer

Summary

EudraCT number	2008-006831-10
Trial protocol	DE FR SE BE PT SK DK AT NL FI PL IT GR CZ ES GB
Global end of trial date	15 September 2016

Results information

Result version number	v3 (current)
This version publication date	13 December 2021
First version publication date	22 March 2015
Version creation reason	
Summary attachment (see zip file)	1199.15 (1199.15_c03055581-01_PR_DR.pdf)

Trial information

Trial identification

Sponsor protocol code	1199.15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01015118
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	26 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2013
Global end of trial reached?	Yes
Global end of trial date	15 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to evaluate whether nintedanib (BIBF1120), added to standard chemotherapy with paclitaxel and carboplatin for 6 courses and subsequently in monotherapy, is more effective in prolonging progression-free survival (PFS) than placebo in combination with standard chemotherapy of carboplatin/paclitaxel in patients with advanced epithelial ovarian cancer, defined as Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stages IIB-IV, after primary debulking surgery.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Austria: 36
Country: Number of subjects enrolled	Belgium: 30
Country: Number of subjects enrolled	Czechia: 25
Country: Number of subjects enrolled	Germany: 340
Country: Number of subjects enrolled	Denmark: 43
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	France: 125
Country: Number of subjects enrolled	Greece: 33
Country: Number of subjects enrolled	Italy: 146
Country: Number of subjects enrolled	Norway: 80
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Portugal: 18

Country: Number of subjects enrolled	Poland: 62
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Sweden: 52
Country: Number of subjects enrolled	Finland: 24
Country: Number of subjects enrolled	Slovakia: 77
Country: Number of subjects enrolled	Ukraine: 26
Country: Number of subjects enrolled	United Kingdom: 56
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	United States: 215
Worldwide total number of subjects	1504
EEA total number of subjects	1131

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)	1081
From 65 to 84 years	423
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

1366 patients were randomised for this study.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

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

Blinding implementation details:

This trial had a parallel-group, double-blind, placebocontrolled design.

Arms

Are arms mutually exclusive?	Yes
Arm title	Nintedanib

Arm description:

Patients to receive Nintedanib 200 milligram (mg) soft gelatine capsule, taken orally twice daily, except the day of chemotherapy (carboplatin and paclitaxel) infusion, every 21 days for six courses.

Arm type	Experimental
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Patients to receive Nintedanib 200 mg soft gelatine capsule, taken orally twice daily, except the day of chemotherapy (carboplatin and paclitaxel) infusion, every 21 days for six courses.

Arm title	Placebo

Arm description:

Patients to receive matching placebo soft gelatine capsule identical to those containing Nintedanib, taken orally twice daily, except the day of chemotherapy (carboplatin and paclitaxel) infusion, every 21 days for six courses.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Patients to receive matching placebo soft gelatine capsule identical to those containing Nintedanib, taken orally twice daily, except the day of chemotherapy (carboplatin and paclitaxel) infusion, every 21 days for six courses.

Number of subjects in period 1[1]	Nintedanib	Placebo
Started	911	455
Completed	242	128
Not completed	669	327
Adverse event, serious fatal	9	5
Consent withdrawn by subject	103	27
Other than stated below	42	23
Adverse event, non-fatal	132	28
Worsening or AE of underlying disease	5	4
Progressive disease	364	229
Protocol deviation	5	6
Not treated	9	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication. No Statistical analysis

Baseline characteristics

Reporting groups	
Reporting group title	Nintedanib
Reporting group description:	
Patients to receive Nintedanib 200 milligram (mg) soft gelatine capsule, taken orally twice daily, except the day of chemotherapy (carboplatin and paclitaxel) infusion, every 21 days for six courses.	
Reporting group title	Placebo
Reporting group description:	
Patients to receive matching placebo soft gelatine capsule identical to those containing Nintedanib, taken orally twice daily, except the day of chemotherapy (carboplatin and paclitaxel) infusion, every 21 days for six courses.	

Reporting group values	Nintedanib	Placebo	Total
Number of subjects	911	455	1366
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age Continuous			
Randomised Set (RS): included all randomised patients, regardless of whether or not they had received treatment. Patients were assigned to nintedanib or placebo as randomised.			
Units: years			
arithmetic mean	57.5	56.9	
standard deviation	± 11.0	± 11.1	-
Gender, Male/Female			
Units: Subjects			
Female	911	455	1366
Male	0	0	0

End points

End points reporting groups

Reporting group title	Nintedanib

Reporting group description:

Patients to receive Nintedanib 200 milligram (mg) soft gelatine capsule, taken orally twice daily, except the day of chemotherapy (carboplatin and paclitaxel) infusion, every 21 days for six courses.

Reporting group title	Placebo

Reporting group description:

Patients to receive matching placebo soft gelatine capsule identical to those containing Nintedanib, taken orally twice daily, except the day of chemotherapy (carboplatin and paclitaxel) infusion, every 21 days for six courses.

Primary: PFS based on Investigator Assessment according to modified Response Evaluation Criteria in Solid Tumors, version 1.1 (mRECIST), and additional clinical criteria.

End point title	PFS based on Investigator Assessment according to modified Response Evaluation Criteria in Solid Tumors, version 1.1 (mRECIST), and additional clinical criteria.

End point description:

Progression free survival (PFS) is calculated as the time from randomisation to the date of disease progression, or to the date of death, whichever occurs first according to the Investigator assessment. The primary PFS analysis of this trial was performed when approximately 753 patients had experienced a PFS event Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve for each treatment arm.

End point type	Primary

End point timeframe:

First drug administration to date of disease progression or death whichever occurs first , upto 29 months

End point values	Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[1]	455[2]		
Units: Months				
median (inter-quartile range (Q1-Q3))	17.2 (11.1 to 32.5)	16.6 (10.8 to 30.4)		

Notes:

[1] - Randomised Set (RS)

[2] - Randomised Set (RS)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard ratio (HR), Confidence Interval (CI) and P-value obtained from a proportional-hazards model stratified by Macroscopic residual postoperative tumour (Yes vs. no), the International Federation of Gynecology and Obstetrics (FIGO) Stage (IIB-III vs. IV) and carboplatin level Area under curve 5 (AUC5) vs. Area under curve 6 (AUC6).

Comparison groups	Nintedanib v Placebo

Number of subjects included in analysis	1366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0239
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.98

Primary: PFS based on Investigator Assessment according to modified Response Evaluation Criteria in Solid Tumors, version 1.1 (mRECIST), and additional clinical criteria (follow up analysis).

End point title	PFS based on Investigator Assessment according to modified Response Evaluation Criteria in Solid Tumors, version 1.1 (mRECIST), and additional clinical criteria (follow up analysis).

End point description:

Follow-up analysis was conducted at the time of overall survival analysis. Progression free survival (PFS) is calculated as the time from randomisation to the date of disease progression, or to the date of death, whichever occurs first according to the Investigator assessment. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve for each treatment arm.

End point type	Primary

End point timeframe:

First drug administration to date of disease progression or death whichever occurs first until final Data Base Lock (DBL) 26September16, upto 62 months

End point values	Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[3]	455[4]		
Units: Months				
median (inter-quartile range (Q1-Q3))	17.6 (11.1 to 38.0)	16.6 (10.8 to 37.3)		

Notes:

[3] - Randomised Set (RS)

[4] - Randomised Set (RS)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Hazard ratio (HR), Confidence Interval (CI) and P-value obtained from a proportional-hazards model stratified by Macroscopic residual postoperative tumour (Yes vs. no), the International Federation of Gynecology and Obstetrics (FIGO) Stage (IIB-III vs. IV) and carboplatin level (AUC5 vs. AUC6).

Comparison groups	Nintedanib v Placebo

Number of subjects included in analysis	1366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0286
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	0.98

Secondary: PFS based on Investigator Assessment according to mRECIST version 1.1 (Key secondary endpoint).

End point title	PFS based on Investigator Assessment according to mRECIST version 1.1 (Key secondary endpoint).

End point description:

Progression free survival is calculated as the time from randomisation to the date of disease progression, or to the date of death, whichever occurs first based on the Investigator assessment according to Modified Response Evaluation Criteria (mRECIST), version 1.1. The primary PFS analysis of this trial was performed when approximately 753 patients had experienced a PFS event. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve for each treatment arm.

End point type	Secondary

End point timeframe:

First drug administration to date of disease progression or death whichever occurs first , upto 29 months

End point values	Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911	455		
Units: Months				
median (inter-quartile range (Q1-Q3))	18.3 (11.1 to 32.5)	16.6 (10.8 to 30.4)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

HR, CI and P-value obtained from a proportional-hazards model stratified by Macroscopic residual postoperative tumour (Yes vs. no), the International Federation of Gynecology and Obstetrics (FIGO) Stage (IIB-III vs. IV) and carboplatin level (AUC5 vs. AUC6).

Comparison groups	Nintedanib v Placebo

Number of subjects included in analysis	1366
Analysis specification	Pre-specified
Analysis type	superiority
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.97

Secondary: PFS based on Investigator Assessment according to mRECIST version 1.1 (Key secondary endpoint - follow up analysis).

End point title	PFS based on Investigator Assessment according to mRECIST version 1.1 (Key secondary endpoint - follow up analysis).

End point description:

Follow-up analysis was conducted at the time of overall survival analysis. Progression free survival is calculated as the time from randomisation to the date of disease progression, or to the date of death, whichever occurs first based on the Investigator assessment according to Modified Response Evaluation Criteria (mRECIST), version 1.1. Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve for each treatment arm.

End point type	Secondary

End point timeframe:

First drug administration to date of disease progression or death whichever occurs first until final Data Base Lock (DBL) 26September16, upto 62 months

End point values	Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[5]	455[6]		
Units: Months				
median (inter-quartile range (Q1-Q3))	18.4 (11.1 to 38.5)	16.6 (10.8 to 37.3)		

Notes:

[5] - Randomised Set (RS)

[6] - Randomised Set (RS)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

HR, CI and P-value obtained from a proportional-hazards model stratified by Macroscopic residual postoperative tumour (Yes vs. no), the International Federation of Gynecology and Obstetrics (FIGO) Stage (IIB-III vs. IV) and carboplatin level (AUC5 vs. AUC6).

Comparison groups	Nintedanib v Placebo

Number of subjects included in analysis	1366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0256
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	0.98

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is defined as time from randomization to date of death (irrespective of reason). Median, 25th and 75th percentiles are calculated from an unadjusted Kaplan-Meier curve for each treatment arm. 99999: Not calculable because of insufficient number of participants with events

End point type	Secondary

End point timeframe:

First drug administration to date of death until final DBL 26September16, upto 62 months

End point values	Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[7]	455[8]		
Units: Months				
median (inter-quartile range (Q1-Q3))	62.0 (30.0 to 99999)	62.8 (30.6 to 99999)		

Notes:

[7] - Randomised Set (RS)

[8] - Randomised Set (RS)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

HR, CI and P-value obtained from a proportional-hazards model stratified by Macroscopic residual postoperative tumour (Yes vs. no), the International Federation of Gynecology and Obstetrics (FIGO) Stage (IIB-III vs. IV) and carboplatin level (AUC5 vs. AUC6).

Comparison groups	Nintedanib v Placebo
Number of subjects included in analysis	1366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8653
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.17

Secondary: Time to CA-125 tumour marker progression

End point title	Time to CA-125 tumour marker progression

End point description:

Time to tumour-marker progression was defined as the time from randomisation until the date when Carbohydrate (cancer) antigen (CA-125) values increased to higher than twice the nadir value. CA-125 >=2 x nadir in case nadir value > Upper limit of normal (ULN) or CA-125 >=2 x ULN in case nadir value <= ULN.

End point type	Secondary

End point timeframe:

First drug administration until final DBL 26September16, upto 62 months

End point values	Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[9]	455[10]		
Units: Months				
median (inter-quartile range (Q1-Q3))	16.6 (10.6 to 47.0)	14.1 (8.6 to 42.6)		

Notes:

[9] - Randomised Set (RS)

[10] - Randomised Set (RS)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

HR, CI and P-value obtained from a proportional-hazards model stratified by Macroscopic residual postoperative tumour (Yes vs. no), the International Federation of Gynecology and Obstetrics (FIGO) Stage (IIB-III vs. IV) and carboplatin level (AUC5 vs. AUC6).

Comparison groups	Nintedanib v Placebo
Number of subjects included in analysis	1366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0749
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.01

Secondary: objective response based on Investigator assessment

End point title	objective response based on Investigator assessment

End point description:

Objective tumour response defined as either complete response [CR] or partial response [PR] in patients with at least 1 target lesion reported at baseline

End point type	Secondary

End point timeframe:

First drug administration until final DBL 26September16, upto 62 months

End point values	Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[11]	455[12]		
Units: percentage of participants				
number (not applicable)	74.3	70.2		

Notes:

[11] - Randomised Set (RS) for patients with at least 1 target lesion reported at baseline

[12] - Randomised Set (RS) for patients with at least 1 target lesion reported at baseline

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Odds ratio and p−value are obtained from logistic regression model adjusting for, macroscopic residual postoperative tumour (yes vs. no), the International Federation of Gynecology and Obstetrics (FIGO) stage (IIB−III vs. IV) and carboplatin level (AUC5 vs. AUC6).

Comparison groups	Nintedanib v Placebo
Number of subjects included in analysis	1366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.349
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.82

Secondary: Change in abdominal/gastro-intestinal symptoms over time

End point title	Change in abdominal/gastro-intestinal symptoms over time

End point description:

Change in abdominal/gastro-intestinal over time was calculated on symptoms (scale composite of items 31 to 37 of the European Organisation for Research and Treatment of Cancer Quality of Life

Questionnaire Module for Ovarian Cancer 28 (EORTC QLQ OV-28). As specified in the EORTC scoring manual, for each scale or item, a linear transformation was applied to standardize the raw score to a range from 0 to 100 (high scores represent a high/severe level of symptomatology). Mean presented is Adjusted mean. Adjusted for the stratification factors macroscopic residual postoperative tumour at baseline (yes vs. no), FIGO stage (IIB−III vs IV), and Carboplatin level (AUC5 vs. AUC6).

End point type	Secondary

End point timeframe:

First drug administration until final DBL 26September16, upto 62 months

End point values	Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[13]	455[14]		
Units: units on a scale				
arithmetic mean (standard error)	24.63 (± 0.49)	19.34 (± 0.64)		

Notes:

[13] - Randomised Set (RS) for patients with abdominal/gastro-intestinal symptoms

[14] - Randomised Set (RS) for patients with abdominal/gastro-intestinal symptoms

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Adjusted for the stratification factors macroscopic residual postoperative tumour at baseline (yes vs. no), the International Federation of Gynecology and Obstetrics (FIGO) stage (IIB−III vs IV), and carboplatin level (AUC5 vs. AUC6).

Comparison groups	Nintedanib v Placebo
Number of subjects included in analysis	1366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed effect growth curve model
Parameter estimate	Mean difference (net)
Point estimate	5.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.88
upper limit	6.69
Variability estimate	Standard error of the mean
Dispersion value	0.72

Secondary: Change in Global Health Status/ Quality of life (QoL) scale over time.

End point title	Change in Global Health Status/ Quality of life (QoL) scale over time.

End point description:

Change in Global Health Status/ QoL over time was calculated on Global Health Status/QoL scale (composite of items 29 and 30 of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30 (EORTC QLQ-C30) as a general measure. As specified in the EORTC scoring manual, for each scale or item, a linear transformation was applied to standardize the raw score

to a range from 0 to 100 (high scores represent a high/healthy level of functioning). Mean presented is Adjusted mean. Adjusted for the stratification factors macroscopic residual postoperative tumour at baseline (yes vs. no), FIGO stage (IIB−III vs IV), and Carboplatin level (AUC5 vs. AUC6).

End point type	Secondary

End point timeframe:

First drug administration until final DBL 26September16, upto 62 months

End point values	Nintedanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	911[15]	455[16]		
Units: units on a scale				
arithmetic mean (standard error)	68.79 (± 0.48)	70.67 (± 0.65)		

Notes:

[15] - Randomised Set (RS) for patients with global health status/QoL

[16] - Randomised Set (RS) for patients with global health status/QoL

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Adjusted for the stratification factors macroscopic residual postoperative tumour at baseline (yes vs. no), the International Federation of Gynecology and Obstetrics (FIGO) stage (IIB−III vs IV), and carboplatin level (AUC5 vs. AUC6).

Comparison groups	Nintedanib v Placebo
Number of subjects included in analysis	1366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0124
Method	Mixed effect growth curve model
Parameter estimate	Mean difference (net)
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.35
upper limit	-0.41
Variability estimate	Standard error of the mean
Dispersion value	0.75

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 28 days after the last drug administration.

Adverse event reporting additional description:

Adverse Events were reported for the treated patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients to receive matching placebo soft gelatine capsule identical to those containing Nintedanib, taken orally twice daily, except the day of chemotherapy (carboplatin and paclitaxel) infusion, every 21 days for six courses.

Reporting group title	Nintedanib

Reporting group description:

Patients to receive Nintedanib 200 milligram (mg) soft gelatine capsule, taken orally twice daily, except the day of chemotherapy (carboplatin and paclitaxel) infusion, every 21 days for six courses

Serious adverse events	Placebo	Nintedanib	
Total subjects affected by serious adverse events			
subjects affected / exposed	157 / 450 (34.89%)	379 / 902 (42.02%)	
number of deaths (all causes)	203	402	
number of deaths resulting from adverse events	16	30	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal wall neoplasm			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of thyroid gland			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bladder cancer			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain cancer metastatic			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 450 (0.22%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer recurrent			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchioloalveolar carcinoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar tumour			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	7 / 450 (1.56%)	15 / 902 (1.66%)	
occurrences causally related to treatment / all	0 / 7	0 / 15	
deaths causally related to treatment / all	0 / 7	0 / 15	
Metastases to central nervous system			
subjects affected / exposed	2 / 450 (0.44%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to large intestine			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to reproductive organ			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to small intestine			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian cancer			

subjects affected / exposed	2 / 450 (0.44%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian epithelial cancer			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic neoplasm			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal neoplasm			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary vein thrombosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	5 / 450 (1.11%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	2 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 450 (0.00%)	5 / 902 (0.55%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 450 (0.22%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	2 / 450 (0.44%)	6 / 902 (0.67%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	1 / 450 (0.22%)	6 / 902 (0.67%)	
occurrences causally related to treatment / all	0 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous occlusion			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheter placement			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central venous catheter removal			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemotherapy			

subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystectomy			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytoreductive surgery			
subjects affected / exposed	2 / 450 (0.44%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileostomy			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal resection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laparotomy			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine anastomosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal operation			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (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	2 / 450 (0.44%)	13 / 902 (1.44%)	
occurrences causally related to treatment / all	0 / 2	7 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haematoma			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	4 / 450 (0.89%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Fatigue			
subjects affected / exposed	2 / 450 (0.44%)	10 / 902 (1.11%)	
occurrences causally related to treatment / all	0 / 3	3 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	5 / 450 (1.11%)	17 / 902 (1.88%)	
occurrences causally related to treatment / all	2 / 5	2 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hernia			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site erythema			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (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 / 450 (0.22%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodule			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			

subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 450 (0.44%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 450 (1.78%)	23 / 902 (2.55%)	
occurrences causally related to treatment / all	2 / 8	1 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 450 (0.44%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Surgical failure			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactoid reaction			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media allergy			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	3 / 450 (0.67%)	9 / 902 (1.00%)	
occurrences causally related to treatment / all	0 / 3	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical polyp			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine fistula			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal fistula			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	2 / 450 (0.44%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal ulceration			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
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			
Asthma			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 450 (0.89%)	10 / 902 (1.11%)	
occurrences causally related to treatment / all	0 / 5	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			

subjects affected / exposed	1 / 450 (0.22%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 450 (0.22%)	6 / 902 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 450 (0.00%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 450 (1.11%)	11 / 902 (1.22%)	
occurrences causally related to treatment / all	3 / 6	6 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 450 (0.44%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 450 (0.22%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conversion disorder			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 450 (0.00%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	1 / 450 (0.22%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biopsy vulva			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 450 (0.00%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrin D dimer increased			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 450 (0.00%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
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	2 / 450 (0.44%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 450 (0.00%)	5 / 902 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 450 (0.00%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 450 (0.22%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (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	2 / 450 (0.44%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured coccyx			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 450 (0.22%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iatrogenic injury			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (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	4 / 450 (0.89%)	8 / 902 (0.89%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation of wound			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural diarrhoea			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative fever			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scar			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginal injury			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	2 / 450 (0.44%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Cancer gene carrier			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 450 (0.00%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 450 (0.44%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiovascular disorder			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (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	1 / 450 (0.22%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachyarrhythmia			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asterixis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 450 (0.22%)	5 / 902 (0.55%)	
occurrences causally related to treatment / all	0 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 450 (0.00%)	5 / 902 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemianopia homonymous			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
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 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 450 (0.22%)	6 / 902 (0.67%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	9 / 450 (2.00%)	36 / 902 (3.99%)	
occurrences causally related to treatment / all	1 / 13	5 / 43	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 450 (1.33%)	20 / 902 (2.22%)	
occurrences causally related to treatment / all	0 / 6	3 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 450 (0.22%)	8 / 902 (0.89%)	
occurrences causally related to treatment / all	0 / 1	3 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	2 / 450 (0.44%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic haemolytic anaemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	6 / 450 (1.33%)	24 / 902 (2.66%)	
occurrences causally related to treatment / all	1 / 8	7 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 450 (0.22%)	8 / 902 (0.89%)	
occurrences causally related to treatment / all	1 / 1	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic vein thrombosis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	6 / 450 (1.33%)	21 / 902 (2.33%)	
occurrences causally related to treatment / all	1 / 7	5 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			

subjects affected / exposed	2 / 450 (0.44%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal discomfort			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	2 / 450 (0.44%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	6 / 450 (1.33%)	30 / 902 (3.33%)	
occurrences causally related to treatment / all	3 / 7	7 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 450 (0.00%)	8 / 902 (0.89%)	
occurrences causally related to treatment / all	0 / 0	5 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous ulcer			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	8 / 450 (1.78%)	14 / 902 (1.55%)	
occurrences causally related to treatment / all	0 / 19	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 450 (0.44%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			

subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	10 / 450 (2.22%)	13 / 902 (1.44%)	
occurrences causally related to treatment / all	1 / 14	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 450 (1.78%)	41 / 902 (4.55%)	
occurrences causally related to treatment / all	3 / 8	39 / 48	
deaths causally related to treatment / all	0 / 0	1 / 1	
Diverticulum intestinal			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			

subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula of small intestine			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Functional gastrointestinal disorder			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 450 (0.44%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	8 / 450 (1.78%)	17 / 902 (1.88%)	
occurrences causally related to treatment / all	0 / 9	4 / 19	
deaths causally related to treatment / all	0 / 2	0 / 1	
Impaired gastric emptying			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	4 / 450 (0.89%)	7 / 902 (0.78%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 450 (0.22%)	5 / 902 (0.55%)	
occurrences causally related to treatment / all	0 / 1	5 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intussusception			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	10 / 450 (2.22%)	24 / 902 (2.66%)	
occurrences causally related to treatment / all	3 / 12	13 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	4 / 450 (0.89%)	12 / 902 (1.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	2 / 450 (0.44%)	8 / 902 (0.89%)	
occurrences causally related to treatment / all	0 / 2	3 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Umbilical hernia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	12 / 450 (2.67%)	33 / 902 (3.66%)	
occurrences causally related to treatment / all	5 / 13	16 / 37	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatomyositis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin erosion			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticarial vasculitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 450 (0.67%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	1 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bladder tamponade			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 450 (0.44%)	7 / 902 (0.78%)	
occurrences causally related to treatment / all	1 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incontinence			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	1 / 450 (0.22%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 450 (0.00%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 450 (0.00%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital fistula			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicocutaneous fistula			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic nodular goitre			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
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			
Arthralgia			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	2 / 450 (0.44%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 450 (0.44%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 450 (0.00%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
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 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	2 / 450 (0.44%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 450 (0.44%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (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			
Abdominal abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Beta haemolytic streptococcal infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 450 (0.00%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 450 (0.00%)	6 / 902 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	3 / 450 (0.67%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis bacterial			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 450 (0.67%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 450 (0.22%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 450 (0.22%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infection			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 450 (0.22%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pharyngeal abscess			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 450 (0.67%)	6 / 902 (0.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			

subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulpitis dental			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 450 (0.44%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 450 (0.44%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 450 (0.22%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Septic shock			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			

subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdiaphragmatic abscess			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 450 (0.22%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 450 (0.67%)	17 / 902 (1.88%)	
occurrences causally related to treatment / all	0 / 3	3 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (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 enterococcal			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 450 (0.44%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 450 (0.00%)	4 / 902 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	6 / 450 (1.33%)	21 / 902 (2.33%)	
occurrences causally related to treatment / all	1 / 6	9 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 450 (0.00%)	2 / 902 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 450 (0.22%)	0 / 902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	2 / 450 (0.44%)	6 / 902 (0.67%)	
occurrences causally related to treatment / all	0 / 2	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 450 (0.00%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 450 (0.00%)	3 / 902 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 450 (0.00%)	1 / 902 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Nintedanib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	442 / 450 (98.22%)	891 / 902 (98.78%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	45 / 450 (10.00%)	73 / 902 (8.09%)	
occurrences (all)	55	86	
Hypertension			
subjects affected / exposed	23 / 450 (5.11%)	119 / 902 (13.19%)	
occurrences (all)	24	138	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	65 / 450 (14.44%)	163 / 902 (18.07%)	
occurrences (all)	99	258	
Fatigue			
subjects affected / exposed	201 / 450 (44.67%)	388 / 902 (43.02%)	
occurrences (all)	313	632	
Mucosal inflammation			
subjects affected / exposed	30 / 450 (6.67%)	62 / 902 (6.87%)	
occurrences (all)	38	74	
Oedema peripheral			
subjects affected / exposed	47 / 450 (10.44%)	48 / 902 (5.32%)	
occurrences (all)	53	53	
Pain			
subjects affected / exposed	27 / 450 (6.00%)	35 / 902 (3.88%)	
occurrences (all)	41	45	
Pyrexia			
subjects affected / exposed	46 / 450 (10.22%)	64 / 902 (7.10%)	
occurrences (all)	51	74	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	21 / 450 (4.67%)	58 / 902 (6.43%)	
occurrences (all)	32	70	
Hypersensitivity			
subjects affected / exposed	32 / 450 (7.11%)	53 / 902 (5.88%)	
occurrences (all)	42	64	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	34 / 450 (7.56%)	57 / 902 (6.32%)	
occurrences (all)	42	61	
Dyspnoea			
subjects affected / exposed	55 / 450 (12.22%)	109 / 902 (12.08%)	
occurrences (all)	69	129	
Epistaxis			
subjects affected / exposed	17 / 450 (3.78%)	72 / 902 (7.98%)	
occurrences (all)	20	88	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	27 / 450 (6.00%)	36 / 902 (3.99%)	
occurrences (all)	33	38	
Depression			
subjects affected / exposed	32 / 450 (7.11%)	51 / 902 (5.65%)	
occurrences (all)	35	51	
Insomnia			
subjects affected / exposed	57 / 450 (12.67%)	105 / 902 (11.64%)	
occurrences (all)	71	128	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	49 / 450 (10.89%)	259 / 902 (28.71%)	
occurrences (all)	72	385	
Aspartate aminotransferase increased			
subjects affected / exposed	41 / 450 (9.11%)	219 / 902 (24.28%)	
occurrences (all)	61	330	
Blood alkaline phosphatase increased			
subjects affected / exposed	16 / 450 (3.56%)	74 / 902 (8.20%)	
occurrences (all)	20	99	
Haemoglobin decreased			
subjects affected / exposed	24 / 450 (5.33%)	56 / 902 (6.21%)	
occurrences (all)	38	76	
Neutrophil count decreased			
subjects affected / exposed	23 / 450 (5.11%)	74 / 902 (8.20%)	
occurrences (all)	35	117	
Platelet count decreased			
subjects affected / exposed	17 / 450 (3.78%)	63 / 902 (6.98%)	
occurrences (all)	34	93	
Nervous system disorders			
Dizziness			
subjects affected / exposed	36 / 450 (8.00%)	77 / 902 (8.54%)	
occurrences (all)	44	95	
Dysgeusia			
subjects affected / exposed	37 / 450 (8.22%)	126 / 902 (13.97%)	
occurrences (all)	41	146	
Headache			

subjects affected / exposed	53 / 450 (11.78%)	140 / 902 (15.52%)	
occurrences (all)	107	285	
Neuropathy peripheral			
subjects affected / exposed	85 / 450 (18.89%)	172 / 902 (19.07%)	
occurrences (all)	101	202	
Paraesthesia			
subjects affected / exposed	64 / 450 (14.22%)	100 / 902 (11.09%)	
occurrences (all)	84	124	
Peripheral sensory neuropathy			
subjects affected / exposed	114 / 450 (25.33%)	214 / 902 (23.73%)	
occurrences (all)	148	263	
Polyneuropathy			
subjects affected / exposed	25 / 450 (5.56%)	50 / 902 (5.54%)	
occurrences (all)	28	54	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	129 / 450 (28.67%)	317 / 902 (35.14%)	
occurrences (all)	191	464	
Leukopenia			
subjects affected / exposed	78 / 450 (17.33%)	165 / 902 (18.29%)	
occurrences (all)	164	318	
Neutropenia			
subjects affected / exposed	203 / 450 (45.11%)	419 / 902 (46.45%)	
occurrences (all)	455	885	
Thrombocytopenia			
subjects affected / exposed	87 / 450 (19.33%)	301 / 902 (33.37%)	
occurrences (all)	175	589	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	20 / 450 (4.44%)	55 / 902 (6.10%)	
occurrences (all)	25	61	
Abdominal pain			
subjects affected / exposed	111 / 450 (24.67%)	281 / 902 (31.15%)	
occurrences (all)	186	419	
Abdominal pain upper			

subjects affected / exposed	58 / 450 (12.89%)	125 / 902 (13.86%)	
occurrences (all)	103	176	
Constipation			
subjects affected / exposed	151 / 450 (33.56%)	254 / 902 (28.16%)	
occurrences (all)	250	373	
Diarrhoea			
subjects affected / exposed	114 / 450 (25.33%)	692 / 902 (76.72%)	
occurrences (all)	248	1900	
Dyspepsia			
subjects affected / exposed	24 / 450 (5.33%)	77 / 902 (8.54%)	
occurrences (all)	32	89	
Flatulence			
subjects affected / exposed	9 / 450 (2.00%)	53 / 902 (5.88%)	
occurrences (all)	10	55	
Nausea			
subjects affected / exposed	231 / 450 (51.33%)	583 / 902 (64.63%)	
occurrences (all)	467	1245	
Stomatitis			
subjects affected / exposed	24 / 450 (5.33%)	51 / 902 (5.65%)	
occurrences (all)	30	65	
Vomiting			
subjects affected / exposed	119 / 450 (26.44%)	391 / 902 (43.35%)	
occurrences (all)	187	763	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	278 / 450 (61.78%)	519 / 902 (57.54%)	
occurrences (all)	283	523	
Pruritus			
subjects affected / exposed	32 / 450 (7.11%)	44 / 902 (4.88%)	
occurrences (all)	37	49	
Rash			
subjects affected / exposed	50 / 450 (11.11%)	95 / 902 (10.53%)	
occurrences (all)	64	131	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	137 / 450 (30.44%)	242 / 902 (26.83%)	
occurrences (all)	241	422	
Back pain			
subjects affected / exposed	54 / 450 (12.00%)	83 / 902 (9.20%)	
occurrences (all)	85	99	
Bone pain			
subjects affected / exposed	39 / 450 (8.67%)	62 / 902 (6.87%)	
occurrences (all)	56	91	
Myalgia			
subjects affected / exposed	107 / 450 (23.78%)	201 / 902 (22.28%)	
occurrences (all)	202	365	
Musculoskeletal pain			
subjects affected / exposed	29 / 450 (6.44%)	56 / 902 (6.21%)	
occurrences (all)	49	100	
Pain in extremity			
subjects affected / exposed	56 / 450 (12.44%)	95 / 902 (10.53%)	
occurrences (all)	73	125	
Infections and infestations			
Cystitis			
subjects affected / exposed	17 / 450 (3.78%)	66 / 902 (7.32%)	
occurrences (all)	18	91	
Nasopharyngitis			
subjects affected / exposed	36 / 450 (8.00%)	73 / 902 (8.09%)	
occurrences (all)	40	90	
Urinary tract infection			
subjects affected / exposed	50 / 450 (11.11%)	131 / 902 (14.52%)	
occurrences (all)	72	185	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	63 / 450 (14.00%)	168 / 902 (18.63%)	
occurrences (all)	84	227	
Hypokalaemia			
subjects affected / exposed	25 / 450 (5.56%)	85 / 902 (9.42%)	
occurrences (all)	31	132	
Hypomagnesaemia			

subjects affected / exposed occurrences (all)	25 / 450 (5.56%) 38	92 / 902 (10.20%) 133	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2011	1)Details of translational substudy included in study design. Participation was not prerequisite for participation in study as whole.A separate informed consent was required for patients wants to participate in substudy.2)Inclusion criterion6 amended to include appropriate surgical intervention in patients with stageIIIC disease by laparotomy with intention for maximum surgical effort at cytoreduction &adequate staging but no or only limited actual debulking for disease if disease was intraoperatively not considered amenable to maximal cytoreduction,& no surgery was planned prior to disease progression 3)Correction of calculation of maximal dosing of carboplatin based on creatinine clearance.4)Revision of premedication needed prior to dosing with paclitaxel. Premedication schedules vary between hospitals & were considered acceptable as long as steroid in equivalent doses was part of premedication regimen.The revised regimen presented was considered recommendation &could be adapted.5)Criteria for initiation of &re-treatment with combination therapy were revised to be consistent with exclusion criteria & to note that deviations should be iscussed & agreed with sponsor.6)With amendment,it was allowed to replace the chest X-ray to be performed at baseline by chest Computed tomography(CT)scan.7)CA-125: To allow treatment decisions based on this tumour marker,results had to be available at visit. Due to long half-life of glycoprotein,7 days was considered appropriate timeframe.8)Lipase was no longer required for routine clinical laboratory safety analyses since an elevation of lipase was clinically only relevant in conjunction with abdominal symptoms. In case new or worsening abdominal symptoms were present, criteria for malignant bowel obstruction had to be assessed. With the amendment,only 1 coagulation parameters Quick, Prothrombin time (PT) or International normalised ratio(INR) to determined & creatinine to determined during combination courses.
15 September 2014	1) Global protocol amendment 2 introduced an additional analysis to be performed in October 2014, approximately 18 months after the primary PFS analysis [c01799511-02]. An update of the trial analysis was to be conducted, focusing on overall survival, but also including other efficacy and safety endpoints. The analysis was to be performed in the pre-defined subgroups along with additional exploratory subgroups identified at the time of the primary PFS analysis. Results of this additional analysis were reported in a synoptic interim report [c03038398-01]. 2) The reason for implementing this additional analysis was that data for OS were immature at the time of the primary analysis due to a low number of OS events. The time point was chosen based on the projection of OS event accumulation allowing for a more reliable estimate of any treatment effects. Potential new information gained from this additional analysis was considered highly relevant for the planning of further study activities to confirm clinically meaningful efficacy of nintedanib in Ovarian cancer(OC).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported