Clinical trial results:
A Phase 3 Randomized, Double-Blind Study of PF-06439535 Plus Paclitaxel-Carboplatin and Bevacizumab Plus Paclitaxel-Carboplatin for the First-Line Treatment of Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer

Summary

EudraCT number	2014-003878-16
Trial protocol	SK NL CZ DE ES PL HU GR HR IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	23 May 2018
First version publication date	23 May 2018

Trial information

Trial identification

Sponsor protocol code	B7391003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	13 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the confirmed objective response rate (ORR) by Week 19 following treatment with PF-06439535 in combination with paclitaxel and carboplatin to bevacizumab-EU plus paclitaxel and carboplatin in subjects who had not received previous treatment for advanced non-small cell lung cancer (NSCLC).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Chile: 10
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Greece: 18
Country: Number of subjects enrolled	Hungary: 52
Country: Number of subjects enrolled	India: 30
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Romania: 62
Country: Number of subjects enrolled	Russian Federation: 176

Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Thailand: 15
Country: Number of subjects enrolled	Turkey: 32
Country: Number of subjects enrolled	Ukraine: 152
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	719
EEA total number of subjects	240

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)	456
From 65 to 84 years	261
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 719 subjects were enrolled in this study, and 5 of them didn't receive study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-06439535

Arm description:

Subjects received up to a maximum of 6 cycles of PF-06439535 (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m*2) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by PF-06439535 monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed in response to toxicity. Paclitaxel was administered before carboplatin.

Arm type	Experimental
Investigational medicinal product name	PF-06439535
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

PF-06439535 was administered once at the start of each 21-day cycle via intravenous (IV) infusion. The initial dose level was 15 mg/kg and dose reduction was allowed in response to toxicity.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered once on Day 1 of each 21-day cycle via intravenous (IV) infusion after PF-06439535 administration. The initial dose level was 200 mg/m*2 and dose reduction was allowed in response to toxicity.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was administered once on Day 1 of each 21-day cycle via intravenous (IV) infusion after paclitaxel administration. The initial dose level was AUC 6 and dose reduction was allowed in response to toxicity.

Arm title	Bevacizumab-EU

Arm description:

Subjects received up to a maximum of 6 cycles of Bevacizumab-EU (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m*2) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by Bevacizumab-EU monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed in response to toxicity. Paclitaxel was administered before carboplatin.

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab-EU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab-EU was administered once at the start of each 21-day cycle via intravenous (IV) infusion. The initial dose level was 15 mg/kg and dose reduction was allowed in response to toxicity.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin was administered once on Day 1 of each 21-day cycle via intravenous (IV) infusion after paclitaxel administration. The initial dose level was AUC 6 and dose reduction was allowed in response to toxicity.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered once on Day 1 of each 21-day cycle via intravenous (IV) infusion after Bevacizumab-EU administration. The initial dose level was 200 mg/m*2 and dose reduction was allowed in response to toxicity.

Number of subjects in period 1	PF-06439535	Bevacizumab-EU
Started	358	361
Received treatment	356	358
Completed	40	39
Not completed	318	322
Adverse event, serious fatal	109	99
Consent withdrawn by subject	13	10
Study ongoing	179	194
Randomized but did not receive treatment	2	3
Global Deterioration Of Health Status	-	2
Unspecified	1	1
Lost to follow-up	9	11

Objective Progression Or Relapse	3	-
Protocol deviation	2	2

Baseline characteristics

Reporting groups	
Reporting group title	PF-06439535

Reporting group description:

Subjects received up to a maximum of 6 cycles of PF-06439535 (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m*2) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by PF-06439535 monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed in response to toxicity. Paclitaxel was administered before carboplatin.

Reporting group title	Bevacizumab-EU

Reporting group description:

Subjects received up to a maximum of 6 cycles of Bevacizumab-EU (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m*2) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by Bevacizumab-EU monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed in response to toxicity. Paclitaxel was administered before carboplatin.

Reporting group values	PF-06439535	Bevacizumab-EU	Total
Number of subjects	358	361	719
Age, Customized Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age <37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days - 23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	217	239	456
From 65-84 years	139	122	261
85 years and over	2	0	2
Age Continuous Units: years			
arithmetic mean	61.7	60.9	
standard deviation	± 9.5	± 8.9	-
Sex/Gender, Customized Units: Subjects			
Female|	121	131	252
Male|	237	230	467
Race/Ethnicity, Customized Units: Subjects			
WHITE|	319	319	638
BLACK|	3	1	4
ASIAN|	36	40	76
OTHER|	0	1	1

End points

End points reporting groups

Reporting group title	PF-06439535

Reporting group description:

Subjects received up to a maximum of 6 cycles of PF-06439535 (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m*2) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by PF-06439535 monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed in response to toxicity. Paclitaxel was administered before carboplatin.

Reporting group title	Bevacizumab-EU

Reporting group description:

Subjects received up to a maximum of 6 cycles of Bevacizumab-EU (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m*2) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by Bevacizumab-EU monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed in response to toxicity. Paclitaxel was administered before carboplatin.

Primary: Objective Response Rate (ORR) by Week 19

End point title	Objective Response Rate (ORR) by Week 19

End point description:

ORR refers to percentage of subjects who achieved complete response (CR) or partial response (PR) by Week 19 of the study in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 which was subsequently confirmed by Week 25. A subject achieved CR if both target and non-target lesions achieved CR, no new lesions; achieved PR if target lesions achieved CR or PR, non-target lesions were assessed as non-CR/non-PD (progressive disease), indeterminate or missing, and no new lesions. For target lesions, CR: complete disappearance of all target lesions except nodal disease (target nodes must decrease to normal size); PR: >= 30% decrease under baseline of the sum of diameters of all target measurable lesions. For non-target lesions, CR: disappearance of all non-target lesions and normalization of tumor marker levels and all lymph nodes must be normal in size; non-CR/non-PD: persistence of any non-target lesions and/or tumor marker levels above the normal limits.

End point type	Primary

End point timeframe:

25 weeks

End point values	PF-06439535	Bevacizumab-EU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358	361		
Units: percentage of subjects				
number (confidence interval 95%)	45.3 (40.01 to 50.57)	44.6 (39.40 to 49.89)		

Statistical analyses

Statistical analysis title	PF-06439535 vs Bevacizumab-EU in Risk Difference
Comparison groups	PF-06439535 v Bevacizumab-EU
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk difference (RD)
Point estimate	0.6531
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.608
upper limit	7.9082

Statistical analysis title	Risk Ratio: PF-06439535 vs Bevacizumab-EU (95% CI)
Comparison groups	PF-06439535 v Bevacizumab-EU
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	1.0146
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8628
upper limit	1.1933

Statistical analysis title	Risk Ratio: PF-06439535 vs Bevacizumab-EU (90% CI)
Comparison groups	PF-06439535 v Bevacizumab-EU
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Risk ratio (RR)
Point estimate	1.0146
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8856
upper limit	1.1625

Adverse events

Adverse events information

Timeframe for reporting adverse events:

25 weeks

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another subject, or one subject may have experienced both a serious and non-serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	PF-06439535

Reporting group description:

Subjects received up to a maximum of 6 cycles of PF-06439535 (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m*2) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by PF-06439535 monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed in response to toxicity. Paclitaxel was administered before carboplatin.

Reporting group title	Total

Reporting group description:

This reporting group include all subjects who received at least 1 dose of study treatment from PF-06439535 and Bevacizumab-EU groups.

Reporting group title	Bevacizumab-EU

Reporting group description:

Subjects received up to a maximum of 6 cycles of Bevacizumab-EU (initial dose was 15 mg/kg) plus paclitaxel (initial dose was 200 mg/m*2) and carboplatin (initial dose was AUC 6, based on subject's pre-existing renal function and desired platelet nadir), followed by Bevacizumab-EU monotherapy until disease progression, unacceptable toxicity, discretion of the investigator, regulatory request, death, withdrawal of consent occurred. All 3 drugs were given by intravenous (IV) infusion on Day 1 in each 21-day cycle and dose reduction was allowed in response to toxicity. Paclitaxel was administered before carboplatin.

Serious adverse events	PF-06439535	Total	Bevacizumab-EU
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 356 (21.91%)	152 / 714 (21.29%)	74 / 358 (20.67%)
number of deaths (all causes)	25	48	23
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone cancer metastatic			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neoplasm progression			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Vascular disorders			
Brachiocephalic vein thrombosis			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism arterial			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Haemorrhage			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemia			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Subgaleal haematoma			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	4 / 356 (1.12%)	5 / 714 (0.70%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	3 / 5	3 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 356 (0.56%)	4 / 714 (0.56%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 4	0 / 2
Disease progression			
subjects affected / exposed	3 / 356 (0.84%)	9 / 714 (1.26%)	6 / 358 (1.68%)
occurrences causally related to treatment / all	0 / 3	0 / 9	0 / 6
deaths causally related to treatment / all	0 / 2	0 / 6	0 / 4
General physical health deterioration			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	2 / 356 (0.56%)	3 / 714 (0.42%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 356 (0.84%)	5 / 714 (0.70%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	1 / 3	1 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	2 / 356 (0.56%)	3 / 714 (0.42%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	2 / 2	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	2 / 356 (0.56%)	4 / 714 (0.56%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	2 / 2	2 / 5	0 / 3
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary embolism			
subjects affected / exposed	7 / 356 (1.97%)	9 / 714 (1.26%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	2 / 7	4 / 9	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	3 / 356 (0.84%)	6 / 714 (0.84%)	3 / 358 (0.84%)
occurrences causally related to treatment / all	1 / 3	2 / 6	1 / 3
deaths causally related to treatment / all	1 / 2	2 / 5	1 / 3
Pulmonary oedema			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Respiratory failure			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fracture			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Acute myocardial infarction			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	1 / 1	1 / 2	0 / 1
Angina unstable			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			

subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiovascular insufficiency			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Headache			

subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 356 (0.00%)	3 / 714 (0.42%)	3 / 358 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Mononeuropathy			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 356 (0.56%)	7 / 714 (0.98%)	5 / 358 (1.40%)
occurrences causally related to treatment / all	3 / 3	3 / 9	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	5 / 356 (1.40%)	12 / 714 (1.68%)	7 / 358 (1.96%)
occurrences causally related to treatment / all	2 / 7	3 / 14	1 / 7
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Leukopenia			
subjects affected / exposed	2 / 356 (0.56%)	2 / 714 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	4 / 356 (1.12%)	10 / 714 (1.40%)	6 / 358 (1.68%)
occurrences causally related to treatment / all	1 / 5	6 / 13	5 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	3 / 356 (0.84%)	6 / 714 (0.84%)	3 / 358 (0.84%)
occurrences causally related to treatment / all	2 / 5	4 / 8	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 356 (0.56%)	4 / 714 (0.56%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 356 (0.00%)	2 / 714 (0.28%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic colitis			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			

subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	2 / 356 (0.56%)	2 / 714 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Bone pain			
subjects affected / exposed	0 / 356 (0.00%)	2 / 714 (0.28%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal infection			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated tuberculosis			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	3 / 356 (0.84%)	3 / 714 (0.42%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infection			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 356 (0.28%)	3 / 714 (0.42%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 356 (0.28%)	2 / 714 (0.28%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral fungal infection			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural infection			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	8 / 356 (2.25%)	14 / 714 (1.96%)	6 / 358 (1.68%)
occurrences causally related to treatment / all	3 / 11	3 / 17	0 / 6
deaths causally related to treatment / all	1 / 2	1 / 2	0 / 0
Respiratory tract infection			

subjects affected / exposed	2 / 356 (0.56%)	2 / 714 (0.28%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 356 (0.00%)	2 / 714 (0.28%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 356 (0.28%)	3 / 714 (0.42%)	2 / 358 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	1 / 356 (0.28%)	1 / 714 (0.14%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	4 / 356 (1.12%)	4 / 714 (0.56%)	0 / 358 (0.00%)
occurrences causally related to treatment / all	3 / 5	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 356 (0.00%)	1 / 714 (0.14%)	1 / 358 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1

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

Non-serious adverse events	PF-06439535	Total	Bevacizumab-EU
Total subjects affected by non-serious adverse events			
subjects affected / exposed	337 / 356 (94.66%)	674 / 714 (94.40%)	337 / 358 (94.13%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	49 / 356 (13.76%)	86 / 714 (12.04%)	37 / 358 (10.34%)
occurrences (all)	81	131	50
Aspartate aminotransferase increased			
subjects affected / exposed	42 / 356 (11.80%)	76 / 714 (10.64%)	34 / 358 (9.50%)
occurrences (all)	76	130	54
Blood alkaline phosphatase increased			
subjects affected / exposed	27 / 356 (7.58%)	56 / 714 (7.84%)	29 / 358 (8.10%)
occurrences (all)	39	81	42
Platelet count decreased			
subjects affected / exposed	22 / 356 (6.18%)	40 / 714 (5.60%)	18 / 358 (5.03%)
occurrences (all)	29	65	36

Weight decreased			
subjects affected / exposed	31 / 356 (8.71%)	56 / 714 (7.84%)	25 / 358 (6.98%)
occurrences (all)	36	68	32
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	11 / 356 (3.09%)	29 / 714 (4.06%)	18 / 358 (5.03%)
occurrences (all)	15	36	21
Vascular disorders			
Hypertension			
subjects affected / exposed	55 / 356 (15.45%)	109 / 714 (15.27%)	54 / 358 (15.08%)
occurrences (all)	77	178	101
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 356 (7.87%)	63 / 714 (8.82%)	35 / 358 (9.78%)
occurrences (all)	33	75	42
Neuropathy peripheral			
subjects affected / exposed	51 / 356 (14.33%)	115 / 714 (16.11%)	64 / 358 (17.88%)
occurrences (all)	64	150	86
Paraesthesia			
subjects affected / exposed	40 / 356 (11.24%)	71 / 714 (9.94%)	31 / 358 (8.66%)
occurrences (all)	61	97	36
Peripheral sensory neuropathy			
subjects affected / exposed	34 / 356 (9.55%)	80 / 714 (11.20%)	46 / 358 (12.85%)
occurrences (all)	44	114	70
Polyneuropathy			
subjects affected / exposed	23 / 356 (6.46%)	42 / 714 (5.88%)	19 / 358 (5.31%)
occurrences (all)	34	56	22
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	99 / 356 (27.81%)	203 / 714 (28.43%)	104 / 358 (29.05%)
occurrences (all)	180	371	191
Leukopenia			
subjects affected / exposed	26 / 356 (7.30%)	55 / 714 (7.70%)	29 / 358 (8.10%)
occurrences (all)	42	94	52
Neutropenia			

subjects affected / exposed	59 / 356 (16.57%)	123 / 714 (17.23%)	64 / 358 (17.88%)
occurrences (all)	129	260	131
Thrombocytopenia			
subjects affected / exposed	54 / 356 (15.17%)	118 / 714 (16.53%)	64 / 358 (17.88%)
occurrences (all)	115	234	119
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	43 / 356 (12.08%)	83 / 714 (11.62%)	40 / 358 (11.17%)
occurrences (all)	75	136	61
Fatigue			
subjects affected / exposed	70 / 356 (19.66%)	137 / 714 (19.19%)	67 / 358 (18.72%)
occurrences (all)	102	184	82
Pyrexia			
subjects affected / exposed	20 / 356 (5.62%)	42 / 714 (5.88%)	22 / 358 (6.15%)
occurrences (all)	25	59	34
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	37 / 356 (10.39%)	64 / 714 (8.96%)	27 / 358 (7.54%)
occurrences (all)	43	79	36
Diarrhoea			
subjects affected / exposed	44 / 356 (12.36%)	90 / 714 (12.61%)	46 / 358 (12.85%)
occurrences (all)	55	117	62
Nausea			
subjects affected / exposed	70 / 356 (19.66%)	136 / 714 (19.05%)	66 / 358 (18.44%)
occurrences (all)	110	217	107
Vomiting			
subjects affected / exposed	40 / 356 (11.24%)	72 / 714 (10.08%)	32 / 358 (8.94%)
occurrences (all)	49	85	36
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 356 (10.11%)	76 / 714 (10.64%)	40 / 358 (11.17%)
occurrences (all)	43	91	48
Dyspnoea			
subjects affected / exposed	29 / 356 (8.15%)	59 / 714 (8.26%)	30 / 358 (8.38%)
occurrences (all)	34	70	36
Epistaxis			

subjects affected / exposed	39 / 356 (10.96%)	69 / 714 (9.66%)	30 / 358 (8.38%)
occurrences (all)	48	92	44
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	166 / 356 (46.63%)	330 / 714 (46.22%)	164 / 358 (45.81%)
occurrences (all)	215	446	231
Rash			
subjects affected / exposed	8 / 356 (2.25%)	28 / 714 (3.92%)	20 / 358 (5.59%)
occurrences (all)	9	36	27
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	24 / 356 (6.74%)	55 / 714 (7.70%)	31 / 358 (8.66%)
occurrences (all)	40	102	62
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	39 / 356 (10.96%)	80 / 714 (11.20%)	41 / 358 (11.45%)
occurrences (all)	79	148	69
Bone pain			
subjects affected / exposed	25 / 356 (7.02%)	47 / 714 (6.58%)	22 / 358 (6.15%)
occurrences (all)	58	103	45
Myalgia			
subjects affected / exposed	54 / 356 (15.17%)	102 / 714 (14.29%)	48 / 358 (13.41%)
occurrences (all)	131	237	106
Pain in extremity			
subjects affected / exposed	15 / 356 (4.21%)	38 / 714 (5.32%)	23 / 358 (6.42%)
occurrences (all)	23	52	29
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	46 / 356 (12.92%)	90 / 714 (12.61%)	44 / 358 (12.29%)
occurrences (all)	72	135	63

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2015	Protocol was amended to incorporate feedback from investigators, regulatory agencies, and protocol template updates.
10 June 2016	For EU, primary analysis was changed to risk difference; inclusion and exclusion criteria were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This report reflects data collected up to Week 25, and will be updated within 12 months of study completion.

Notes: