Clinical trial results:
A Randomised, Double Blind, Placebo Controlled, Multicentre Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination With Docetaxel in Comparison With Docetaxel Plus Placebo, as First Line Treatment for Patients With HER2 Negative Metastatic and Locally Recurrent Breast Cancer.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2005-003862-40
Trial protocol	ES BE AT GB SE PT DE LT IT
Global end of trial date	24 October 2013

Results information

Result version number	v2 (current)
This version publication date	15 July 2016
First version publication date	07 August 2015
Version creation reason	• Correction of full data set Data QC after the system unavailability period.
Summary attachment (see zip file)	BO17708_ClinicalTrials.gov receipt (BO17708_CTg results receipt_22Jul15_RF.pdf)

Trial information

Trial identification

Sponsor protocol code	BO17708

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00333775
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. HoffmannLa Roche AG, F. HoffmannLa Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. HoffmannLa Roche AG, F. HoffmannLa Roche AG, +41 616878333, global.trial_information@roche.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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the efficacy and safety of 2 doses of Avastin in combination with docetaxel, versus docetaxel plus placebo, in patients with metastatic HER2 negative breast cancer who were candidates for taxane-based chemotherapy but who had not received prior chemotherapy for metastatic disease. A total of 736 participants were enrolled between March 2006 and April 2007. The last-patient, last-visit was in October 2013.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Spain: 60
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Austria: 31
Country: Number of subjects enrolled	Belgium: 42
Country: Number of subjects enrolled	France: 116
Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Australia: 66
Country: Number of subjects enrolled	Brazil: 33
Country: Number of subjects enrolled	Canada: 71

Country: Number of subjects enrolled	China: 6
Country: Number of subjects enrolled	Mexico: 18
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Panama: 3
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Romania: 14
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	Korea, Republic of: 39
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	Thailand: 19
Worldwide total number of subjects	736
EEA total number of subjects	460

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)	609
From 65 to 84 years	127
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

21 participants randomized to the placebo group received bevacizumab 7.5 mg/kg (n=5) or 15.0 mg/kg (n=16). Disposition, baseline characteristics, and end points for these participants are reported according to randomization group; adverse events for these participants are reported according to treatment received.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Docetaxel 100 mg/m^2 plus placebo

Arm description:

Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Arm type	Control Arm
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel was supplied in 2 vials, 1 containing docetaxel and 1 containing a solvent, for intravenous infusion.

Investigational medicinal product name	Placebo to bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Placebo to bevacizumab was supplied as a sterile liquid for intravenous infusion in single-use vials.

Arm title	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg

Arm description:

Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal

Arm type	Experimental

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel was supplied in 2 vials, 1 containing docetaxel and 1 containing a solvent, for intravenous infusion.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was supplied as a sterile liquid for intravenous infusion in single-use vials.

Arm title	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg

Arm description:

Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Arm type	Experimental
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel was supplied in 2 vials, 1 containing docetaxel and 1 containing a solvent, for intravenous infusion.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was supplied as a sterile liquid for intravenous infusion in single-use vials.

Number of subjects in period 1	Docetaxel 100 mg/m^2 plus placebo	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg
Started	241	248	247
Received Treatment	238	247	245
Completed	0	0	0
Not completed	241	248	247
Death	144	149	143
In follow−up when study stopped	87	92	96
Lost to follow-up	10	7	8

Baseline characteristics

Reporting groups	
Reporting group title	Docetaxel 100 mg/m^2 plus placebo
Reporting group description:	
Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.	
Reporting group title	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg
Reporting group description:	
Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal	
Reporting group title	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg
Reporting group description:	
Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.	

Reporting group values	Docetaxel 100 mg/m^2 plus placebo	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg
Number of subjects	241	248	247
Age categorical Units: Subjects			
Adults (18-64 years)	203	207	199
From 65-84 years	38	41	48
Age continuous Units: years			
arithmetic mean	53.5	53.9	53.6
standard deviation	± 10.47	± 10.61	± 10.78
Gender categorical Units: Subjects			
Female	241	248	247

Reporting group values	Total		
Number of subjects	736		
Age categorical Units: Subjects			
Adults (18-64 years)	609		
From 65-84 years	127		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	736		

End points

End points reporting groups

Reporting group title	Docetaxel 100 mg/m^2 plus placebo
Reporting group description:	
Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.	

Reporting group title	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg
Reporting group description:	
Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal	

Reporting group title	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg
Reporting group description:	
Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.	

Primary: Progression-free Survival

End point title	Progression-free Survival
End point description:	
Progression-free survival was evaluated using Response Evaluation Criteria In Solid Tumors (RECIST 1.0). Progression-free survival was defined as the time from randomization to the time of the first documented disease progression or death, whichever occurred first. Disease progression was defined as ≥ 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since treatment started or the unequivocal progression of existing non-target lesions, or appearance of new lesion(s). Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not.	
End point type	Primary
End point timeframe:	
Baseline to the 15 Sep 2008 cut-off date (up to 2 years, 6 months)	

End point values	Docetaxel 100 mg/m^2 plus placebo	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	241	248	247	
Units: months				
median (confidence interval 95%)	8 (7.2 to 8.3)	8.7 (8.2 to 9.9)	8.8 (8.4 to 10.2)	

Statistical analyses

Statistical analysis title	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg
Comparison groups	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg v Docetaxel 100 mg/m^2 plus placebo
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0318
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.98

Statistical analysis title	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg
Comparison groups	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg v Docetaxel 100 mg/m^2 plus placebo
Number of subjects included in analysis	488
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0036
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.9

Secondary: Percentage of Participants With a Complete Response or a Partial Response

End point title	Percentage of Participants With a Complete Response or a Partial Response

End point description:

Responses were evaluated using the Response Evaluation Criteria in Solid Tumors. A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not. Only participants with measurable disease at Baseline were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline to the 15 Sep 2008 cut-off date (up to 2 years, 6 months)

End point values	Docetaxel 100 mg/m^2 plus placebo	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	207	201	206	
Units: Percentage of participants				
number (confidence interval 95%)				
Complete response	1 (0.1 to 3.4)	3 (1.1 to 6.4)	1 (0.1 to 3.5)	
Partial response	43.5 (36.6 to 50.5)	52.2 (45.1 to 59.3)	62.1 (55.1 to 68.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response was defined as the time from the first documented complete response or partial response to disease progression or death. A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. Responses were evaluated using the Response Evaluation Criteria in Solid Tumors.

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not. Only participants with measurable disease at Baseline who had a complete response or a partial response were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline to the 15 September 2008 cut-off date (up to 2 years, 6 months)

End point values	Docetaxel 100 mg/m^2 plus placebo	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	92[1]	111	130	
Units: months				
median (confidence interval 95%)	6.4 (5.8 to 6.9)	7.2 (6.4 to 9.1)	7 (6.4 to 8.5)	

Notes:

[1] - Only participants with complete response or a partial response were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure

End point description:

Time to treatment failure was defined as time from randomization to the date of disease progression, death, or withdrawal of treatment due to an adverse event, withdrawal of informed consent, insufficient therapeutic response, refusal of treatment/failure to co-operate, or failure to return, whichever occurred first.

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not.

End point type	Secondary

End point timeframe:

Baseline to the 15 September 2008 cut-off date (up to 2 years, 6 months)

End point values	Docetaxel 100 mg/m^2 plus placebo	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	241	248	247	
Units: months				
median (confidence interval 95%)	6.1 (5.6 to 7)	7 (6.1 to 7.7)	7.7 (7.1 to 8)	

Statistical analyses

Statistical analysis title	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg
Comparison groups	Docetaxel 100 mg/m^2 plus placebo v Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1105
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.04

Statistical analysis title	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg

Comparison groups	Docetaxel 100 mg/m^2 plus placebo v Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg
Number of subjects included in analysis	488
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0241
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.97

Secondary: Overall Survival

End point title	Overall Survival

End point description:

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

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not.

999 = Due to the low number of events, the median and lower and/or upper limits of the 95% confidence interval could not be reliably estimated.

End point type	Secondary

End point timeframe:

Baseline to the 15 Sep 2008 cut-off date (up to 2 years, 6 months)

End point values	Docetaxel 100 mg/m^2 plus placebo	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	241	248	247	
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (15.7 to 999)	999 (14.9 to 999)	

Statistical analyses

Statistical analysis title	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg
Comparison groups	Docetaxel 100 mg/m^2 plus placebo v Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg

Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6962
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.37

Statistical analysis title	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
Comparison groups	Docetaxel 100 mg/m^2 plus placebo v Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg
Number of subjects included in analysis	488
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0765
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.04

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to the 24 Oct 2013 cut-off date (up to and 21 day(s) after last dose)

Adverse event reporting additional description:

Safety population: All randomized participants exposed to study medication.

21 participants randomized to the placebo group received bevacizumab 7.5 mg/kg (n=5) or 15.0 mg/kg (n=16). Adverse events for these participants are reported according to treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Docetaxel 100 mg/m^2 plus placebo

Reporting group description:

Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Reporting group title	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg

Reporting group description:

Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Reporting group title	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg

Reporting group description:

Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Serious adverse events	Docetaxel 100 mg/m^2 plus placebo	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	82 / 217 (37.79%)	120 / 261 (45.98%)	106 / 252 (42.06%)
number of deaths (all causes)	7	4	6
number of deaths resulting from adverse events	5	4	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Inflammatory carcinoma of the breast			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non−hodgkin’s lymphoma			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 217 (0.00%)	2 / 261 (0.77%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	2 / 217 (0.92%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microangiopathy			
subjects affected / exposed	2 / 217 (0.92%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism venous			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flushing			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Jugular vein thrombosis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebroplasty			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	3 / 217 (1.38%)	7 / 261 (2.68%)	6 / 252 (2.38%)
occurrences causally related to treatment / all	2 / 3	6 / 9	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	1 / 217 (0.46%)	4 / 261 (1.53%)	6 / 252 (2.38%)
occurrences causally related to treatment / all	0 / 1	4 / 5	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	1 / 217 (0.46%)	2 / 261 (0.77%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	2 / 217 (0.92%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 217 (0.46%)	1 / 261 (0.38%)	0 / 252 (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
Pain			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter related complication			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Face oedema			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ill defined disorder			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Oedema			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	0 / 217 (0.00%)	2 / 261 (0.77%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 217 (0.92%)	3 / 261 (1.15%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	4 / 4	2 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 217 (0.46%)	3 / 261 (1.15%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 217 (1.38%)	2 / 261 (0.77%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Pneumothorax			
subjects affected / exposed	3 / 217 (1.38%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthmatic crisis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum ulceration			

subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood altered			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	2 / 217 (0.92%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dislocation of joint prosthesis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Narcotic intoxication			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural complication			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			

subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriospasm coronary			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block first degree			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia paroxysmal			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 217 (0.00%)	3 / 261 (1.15%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cauda equina syndrome			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cranial nerve palsies multiple			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	21 / 217 (9.68%)	37 / 261 (14.18%)	29 / 252 (11.51%)
occurrences causally related to treatment / all	23 / 23	44 / 44	31 / 32
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Neutropenia			
subjects affected / exposed	4 / 217 (1.84%)	18 / 261 (6.90%)	13 / 252 (5.16%)
occurrences causally related to treatment / all	4 / 4	18 / 19	14 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous detachment			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 217 (1.38%)	8 / 261 (3.07%)	6 / 252 (2.38%)
occurrences causally related to treatment / all	2 / 4	5 / 8	4 / 7
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Abdominal pain			
subjects affected / exposed	4 / 217 (1.84%)	2 / 261 (0.77%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	2 / 4	2 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 217 (0.00%)	4 / 261 (1.53%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	0 / 0	3 / 4	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 217 (0.46%)	3 / 261 (1.15%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 1	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 217 (0.00%)	2 / 261 (0.77%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 217 (0.92%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 217 (0.46%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nausea			
subjects affected / exposed	0 / 217 (0.00%)	2 / 261 (0.77%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			

subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			

subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenal ulcer			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastrointestinal ulcer			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pancreatitis necrotising			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hepatorenal failure			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			

subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin toxicity			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens−Johnson syndrome			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	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 / 217 (0.00%)	2 / 261 (0.77%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	5 / 217 (2.30%)	2 / 261 (0.77%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	5 / 5	1 / 2	2 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	2 / 217 (0.92%)	2 / 261 (0.77%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	2 / 2	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 217 (1.84%)	1 / 261 (0.38%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	2 / 4	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic infection			
subjects affected / exposed	2 / 217 (0.92%)	1 / 261 (0.38%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	2 / 2	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			

subjects affected / exposed	0 / 217 (0.00%)	2 / 261 (0.77%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central line infection			
subjects affected / exposed	0 / 217 (0.00%)	2 / 261 (0.77%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 217 (0.00%)	2 / 261 (0.77%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 217 (0.46%)	1 / 261 (0.38%)	0 / 252 (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
Clostridial infection			
subjects affected / exposed	1 / 217 (0.46%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			
subjects affected / exposed	0 / 217 (0.00%)	2 / 261 (0.77%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 217 (0.46%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	2 / 217 (0.92%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal infection			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorectal infection			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			

subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter bacteraemia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter related infection			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter sepsis			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			

subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nail bed infection			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periodontal infection			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Purulent discharge			

subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Sinusitis			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent related infection			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	3 / 252 (1.19%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	2 / 217 (0.92%)	1 / 261 (0.38%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 217 (0.46%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 217 (0.00%)	0 / 261 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 217 (0.00%)	1 / 261 (0.38%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Docetaxel 100 mg/m^2 plus placebo	Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg	Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	216 / 217 (99.54%)	260 / 261 (99.62%)	251 / 252 (99.60%)
Vascular disorders			
Hypertension			
subjects affected / exposed	32 / 217 (14.75%)	66 / 261 (25.29%)	44 / 252 (17.46%)
occurrences (all)	41	88	60

Hot flush			
subjects affected / exposed	16 / 217 (7.37%)	19 / 261 (7.28%)	16 / 252 (6.35%)
occurrences (all)	21	23	16
Flushing			
subjects affected / exposed	12 / 217 (5.53%)	19 / 261 (7.28%)	15 / 252 (5.95%)
occurrences (all)	20	44	42
Lymphoedema			
subjects affected / exposed	15 / 217 (6.91%)	8 / 261 (3.07%)	19 / 252 (7.54%)
occurrences (all)	16	13	20
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	96 / 217 (44.24%)	109 / 261 (41.76%)	105 / 252 (41.67%)
occurrences (all)	186	226	213
Asthenia			
subjects affected / exposed	83 / 217 (38.25%)	97 / 261 (37.16%)	88 / 252 (34.92%)
occurrences (all)	173	202	183
Mucosal inflammation			
subjects affected / exposed	48 / 217 (22.12%)	78 / 261 (29.89%)	87 / 252 (34.52%)
occurrences (all)	72	135	171
Oedema peripheral			
subjects affected / exposed	89 / 217 (41.01%)	61 / 261 (23.37%)	63 / 252 (25.00%)
occurrences (all)	122	73	84
Pyrexia			
subjects affected / exposed	45 / 217 (20.74%)	63 / 261 (24.14%)	61 / 252 (24.21%)
occurrences (all)	64	87	98
Oedema			
subjects affected / exposed	32 / 217 (14.75%)	21 / 261 (8.05%)	12 / 252 (4.76%)
occurrences (all)	34	23	13
Pain			
subjects affected / exposed	20 / 217 (9.22%)	16 / 261 (6.13%)	16 / 252 (6.35%)
occurrences (all)	20	18	19
Chest pain			
subjects affected / exposed	19 / 217 (8.76%)	20 / 261 (7.66%)	10 / 252 (3.97%)
occurrences (all)	23	22	10
Malaise			

subjects affected / exposed	6 / 217 (2.76%)	15 / 261 (5.75%)	10 / 252 (3.97%)
occurrences (all)	8	15	12
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	47 / 217 (21.66%)	128 / 261 (49.04%)	123 / 252 (48.81%)
occurrences (all)	81	302	287
Cough			
subjects affected / exposed	42 / 217 (19.35%)	61 / 261 (23.37%)	67 / 252 (26.59%)
occurrences (all)	59	83	84
Dyspnoea			
subjects affected / exposed	49 / 217 (22.58%)	60 / 261 (22.99%)	44 / 252 (17.46%)
occurrences (all)	57	70	58
Rhinorrhoea			
subjects affected / exposed	19 / 217 (8.76%)	38 / 261 (14.56%)	26 / 252 (10.32%)
occurrences (all)	37	54	40
Oropharyngeal pain			
subjects affected / exposed	19 / 217 (8.76%)	28 / 261 (10.73%)	27 / 252 (10.71%)
occurrences (all)	26	38	40
Dysphonia			
subjects affected / exposed	10 / 217 (4.61%)	28 / 261 (10.73%)	24 / 252 (9.52%)
occurrences (all)	25	32	47
Pleural effusion			
subjects affected / exposed	13 / 217 (5.99%)	17 / 261 (6.51%)	10 / 252 (3.97%)
occurrences (all)	13	18	10
Nasal dryness			
subjects affected / exposed	3 / 217 (1.38%)	12 / 261 (4.60%)	13 / 252 (5.16%)
occurrences (all)	4	14	22
Psychiatric disorders			
Insomnia			
subjects affected / exposed	34 / 217 (15.67%)	35 / 261 (13.41%)	31 / 252 (12.30%)
occurrences (all)	44	50	38
Depression			
subjects affected / exposed	11 / 217 (5.07%)	13 / 261 (4.98%)	13 / 252 (5.16%)
occurrences (all)	12	14	14
Anxiety			

subjects affected / exposed	8 / 217 (3.69%)	16 / 261 (6.13%)	11 / 252 (4.37%)
occurrences (all)	11	20	11
Investigations			
Weight decreased			
subjects affected / exposed	12 / 217 (5.53%)	30 / 261 (11.49%)	29 / 252 (11.51%)
occurrences (all)	12	31	30
Weight increased			
subjects affected / exposed	16 / 217 (7.37%)	7 / 261 (2.68%)	5 / 252 (1.98%)
occurrences (all)	17	7	6
Nervous system disorders			
Headache			
subjects affected / exposed	56 / 217 (25.81%)	79 / 261 (30.27%)	86 / 252 (34.13%)
occurrences (all)	113	183	198
Dysgeusia			
subjects affected / exposed	59 / 217 (27.19%)	63 / 261 (24.14%)	77 / 252 (30.56%)
occurrences (all)	89	99	120
Peripheral sensory neuropathy			
subjects affected / exposed	60 / 217 (27.65%)	63 / 261 (24.14%)	67 / 252 (26.59%)
occurrences (all)	78	78	90
Paraesthesia			
subjects affected / exposed	40 / 217 (18.43%)	51 / 261 (19.54%)	46 / 252 (18.25%)
occurrences (all)	45	64	71
Neuropathy peripheral			
subjects affected / exposed	30 / 217 (13.82%)	26 / 261 (9.96%)	35 / 252 (13.89%)
occurrences (all)	37	33	44
Dizziness			
subjects affected / exposed	25 / 217 (11.52%)	31 / 261 (11.88%)	26 / 252 (10.32%)
occurrences (all)	34	50	35
Hypoaesthesia			
subjects affected / exposed	11 / 217 (5.07%)	6 / 261 (2.30%)	2 / 252 (0.79%)
occurrences (all)	14	10	2
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	44 / 217 (20.28%)	53 / 261 (20.31%)	51 / 252 (20.24%)
occurrences (all)	102	118	114
Anaemia			

subjects affected / exposed	37 / 217 (17.05%)	32 / 261 (12.26%)	34 / 252 (13.49%)
occurrences (all)	46	45	47
Leukopenia			
subjects affected / exposed	14 / 217 (6.45%)	20 / 261 (7.66%)	21 / 252 (8.33%)
occurrences (all)	23	33	38
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	10 / 217 (4.61%)	15 / 261 (5.75%)	11 / 252 (4.37%)
occurrences (all)	11	19	13
Eye disorders			
Lacrimation increased			
subjects affected / exposed	63 / 217 (29.03%)	120 / 261 (45.98%)	114 / 252 (45.24%)
occurrences (all)	78	149	141
Conjunctivitis			
subjects affected / exposed	11 / 217 (5.07%)	39 / 261 (14.94%)	16 / 252 (6.35%)
occurrences (all)	13	43	18
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	106 / 217 (48.85%)	140 / 261 (53.64%)	143 / 252 (56.75%)
occurrences (all)	206	345	339
Nausea			
subjects affected / exposed	117 / 217 (53.92%)	132 / 261 (50.57%)	115 / 252 (45.63%)
occurrences (all)	243	299	265
Stomatitis			
subjects affected / exposed	60 / 217 (27.65%)	115 / 261 (44.06%)	127 / 252 (50.40%)
occurrences (all)	112	282	294
Constipation			
subjects affected / exposed	64 / 217 (29.49%)	77 / 261 (29.50%)	89 / 252 (35.32%)
occurrences (all)	117	124	195
Vomiting			
subjects affected / exposed	59 / 217 (27.19%)	75 / 261 (28.74%)	64 / 252 (25.40%)
occurrences (all)	88	142	135
Abdominal pain			
subjects affected / exposed	39 / 217 (17.97%)	58 / 261 (22.22%)	45 / 252 (17.86%)
occurrences (all)	58	101	84
Dyspepsia			

subjects affected / exposed	27 / 217 (12.44%)	43 / 261 (16.48%)	36 / 252 (14.29%)
occurrences (all)	37	74	56
Abdominal pain upper			
subjects affected / exposed	34 / 217 (15.67%)	32 / 261 (12.26%)	24 / 252 (9.52%)
occurrences (all)	43	39	29
Haemorrhoids			
subjects affected / exposed	14 / 217 (6.45%)	22 / 261 (8.43%)	22 / 252 (8.73%)
occurrences (all)	16	35	31
Toothache			
subjects affected / exposed	13 / 217 (5.99%)	14 / 261 (5.36%)	13 / 252 (5.16%)
occurrences (all)	13	16	15
Dysphagia			
subjects affected / exposed	12 / 217 (5.53%)	13 / 261 (4.98%)	13 / 252 (5.16%)
occurrences (all)	36	26	26
Dry mouth			
subjects affected / exposed	8 / 217 (3.69%)	12 / 261 (4.60%)	15 / 252 (5.95%)
occurrences (all)	10	15	19
Gingivitis			
subjects affected / exposed	4 / 217 (1.84%)	16 / 261 (6.13%)	11 / 252 (4.37%)
occurrences (all)	8	19	14
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	154 / 217 (70.97%)	183 / 261 (70.11%)	181 / 252 (71.83%)
occurrences (all)	157	192	189
Nail disorder			
subjects affected / exposed	87 / 217 (40.09%)	118 / 261 (45.21%)	118 / 252 (46.83%)
occurrences (all)	93	125	127
Palmar−plantar erythrodysaesthesia syndrome			
subjects affected / exposed	47 / 217 (21.66%)	70 / 261 (26.82%)	80 / 252 (31.75%)
occurrences (all)	58	103	116
Rash			
subjects affected / exposed	43 / 217 (19.82%)	47 / 261 (18.01%)	43 / 252 (17.06%)
occurrences (all)	61	90	58
Dry skin			

subjects affected / exposed	32 / 217 (14.75%)	25 / 261 (9.58%)	33 / 252 (13.10%)
occurrences (all)	34	29	34
Erythema			
subjects affected / exposed	20 / 217 (9.22%)	33 / 261 (12.64%)	26 / 252 (10.32%)
occurrences (all)	45	63	64
Pruritus			
subjects affected / exposed	19 / 217 (8.76%)	23 / 261 (8.81%)	28 / 252 (11.11%)
occurrences (all)	28	29	39
Onycholysis			
subjects affected / exposed	9 / 217 (4.15%)	25 / 261 (9.58%)	21 / 252 (8.33%)
occurrences (all)	9	26	21
Skin exfoliation			
subjects affected / exposed	11 / 217 (5.07%)	20 / 261 (7.66%)	21 / 252 (8.33%)
occurrences (all)	15	31	25
Nail toxicity			
subjects affected / exposed	15 / 217 (6.91%)	12 / 261 (4.60%)	16 / 252 (6.35%)
occurrences (all)	15	12	16
Skin hyperpigmentation			
subjects affected / exposed	8 / 217 (3.69%)	10 / 261 (3.83%)	14 / 252 (5.56%)
occurrences (all)	9	10	18
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	8 / 217 (3.69%)	24 / 261 (9.20%)	12 / 252 (4.76%)
occurrences (all)	10	38	15
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	80 / 217 (36.87%)	88 / 261 (33.72%)	82 / 252 (32.54%)
occurrences (all)	199	181	195
Arthralgia			
subjects affected / exposed	48 / 217 (22.12%)	90 / 261 (34.48%)	74 / 252 (29.37%)
occurrences (all)	92	137	155
Pain in extremity			
subjects affected / exposed	37 / 217 (17.05%)	44 / 261 (16.86%)	56 / 252 (22.22%)
occurrences (all)	54	69	96
Back pain			

subjects affected / exposed	45 / 217 (20.74%)	44 / 261 (16.86%)	36 / 252 (14.29%)
occurrences (all)	54	51	48
Bone pain			
subjects affected / exposed	38 / 217 (17.51%)	42 / 261 (16.09%)	35 / 252 (13.89%)
occurrences (all)	47	65	58
Musculoskeletal pain			
subjects affected / exposed	23 / 217 (10.60%)	36 / 261 (13.79%)	34 / 252 (13.49%)
occurrences (all)	30	57	53
Neck pain			
subjects affected / exposed	8 / 217 (3.69%)	17 / 261 (6.51%)	14 / 252 (5.56%)
occurrences (all)	9	21	17
Musculoskeletal chest pain			
subjects affected / exposed	13 / 217 (5.99%)	12 / 261 (4.60%)	12 / 252 (4.76%)
occurrences (all)	14	12	14
Muscular weakness			
subjects affected / exposed	9 / 217 (4.15%)	9 / 261 (3.45%)	16 / 252 (6.35%)
occurrences (all)	9	10	17
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	23 / 217 (10.60%)	28 / 261 (10.73%)	22 / 252 (8.73%)
occurrences (all)	33	42	29
Nasopharyngitis			
subjects affected / exposed	14 / 217 (6.45%)	35 / 261 (13.41%)	20 / 252 (7.94%)
occurrences (all)	21	49	34
Urinary tract infection			
subjects affected / exposed	18 / 217 (8.29%)	20 / 261 (7.66%)	27 / 252 (10.71%)
occurrences (all)	26	30	32
Influenza			
subjects affected / exposed	12 / 217 (5.53%)	15 / 261 (5.75%)	26 / 252 (10.32%)
occurrences (all)	18	20	43
Rhinitis			
subjects affected / exposed	9 / 217 (4.15%)	18 / 261 (6.90%)	11 / 252 (4.37%)
occurrences (all)	9	23	15
Sinusitis			
subjects affected / exposed	8 / 217 (3.69%)	19 / 261 (7.28%)	10 / 252 (3.97%)
occurrences (all)	8	25	11

Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	58 / 217 (26.73%) 97	85 / 261 (32.57%) 133	78 / 252 (30.95%) 132

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2006	The following changes were made to the protocol at the request of the Paul Ehrlich Institute, Germany: – Investigators were provided with a retrospective analysis of the bleeding risk of full dose anti-coagulated patients receiving bevacizumab. – Investigators were provided with a clear definition of full dose anticoagulation. – ensured that full dose anti-coagulated patients were within the therapeutic ranges and data was collected on the stability of full dose anti-coagulation therapy at baseline or once initiated during study treatment. – Guidance provided on treatment of patients receiving full dose anti-coagulation who suffered from a bleeding event medication. – The 20 patients receiving full dose anti-coagulation to be followed by DSMB were better defined. – for Germany, it was required that patients must have received prior treatment with anthracyclines or alkylating agents in the neo/adjuvant setting. • Text was added that appropriate diagnostic and therapeutic medical treatment including accurate antihypertensive treatment was mandatory for patients developing signs and symptoms of Reversible Posterior Leukoencephalopathy Syndrome • The study title was changed to reflect the study patient population since not only metastatic breast cancer patients were allowed but also locally recurrent breast cancer patients. • The schedule of assessments was changed to accommodate the changes requested by the Paul Ehrlich Institute • The footnotes to Table 2 - were updated • Protocol text was changed to include patients who had received prior neoadjuvant chemotherapy and radiotherapy as this was allowed in addition to patients who had received prior adjuvant chemotherapy and radiotherapy. • Text on study drug management was modified to allow the site to destroy the trial drugs after being used. • The informed consent was updated
19 September 2006	• A washout period for hormone therapy was included in order to reflect the situation of a patient on endocrine treatment as part of an adjuvant treatment. The washout period was reduced from three weeks to two weeks in order to appreciate the fact that such a long treatment interruption may be inappropriate for patients. • Upon the recommendation of DSMB, text on the use of prophylactic antibiotics during Cycle 1 of docetaxel administration for febrile neutropenia prevention was added, and text was added in case of specific chemotherapy adverse event occurrences. • Typographical errors were corrected. • Missing sample procedures following protocol amendment B for patient management of patients on full-dose anticoagulant treatment at study entry was added, and tumor tissue handling and storage was clarified.

24 November 2006	• The protocol was updated to be in line with the latest version of the docetaxel SmPC. • In order to avoid bias at the time of the study's primary endpoint analysis due to a substantial amount of unblinding requests being made, patients considered for treatment with bevacizumab in the open-label phase of the study were allowed to enter into the post-study phase without unblinding, regardless of the first-line treatment (placebo or bevacizumab). • Clarification was given for the assessment of the lesions situated in a previously irradiated area. • Typographical errors were corrected.
10 January 2008	• The text was changed to allow bevacizumab to be given for longer than 32 cycles (96 weeks) until confirmed disease progression, unacceptable toxicity (requiring discontinuation of study treatment) or withdrawal at patient request. • If the analysis of this study (BO17708) showed significant improvements in efficacy, patients randomized to placebo that met specific eligibility criteria were allowed to receive bevacizumab. • Information on how post-study safety data would be analyzed was added. • The procedure for enrollment in the post-study phase was clarified
24 July 2013	• Reason for Change: Text changed from RPLS to PRES to reflect current terminology • Reason for Change: Changes made in this Version H of the protocol have been made to the "end of study" definition with thorough consideration to balance the need for long-term treatment with the organizational goal to reduce drug development costs. Other changes have been made to provide adverse event reporting instructions and contact information for patients continuing in the Optional Post-Study Phase. Overall, additional minor administrative changes have also been made to improve clarity and consistency. This amendment represents cumulative changes to the original protocol. This change affects the Synopsis, Section 3.4, Section 3.5, Section 5.3, Section 6.1, Section 7.2.2, and Appendix 15 o Synopsis - Length of Study o Section 3.4 End of Study o Section 3.5 Provision of Bevacizumab for Patients Randomized to the Placebo Arm o Section 5.3 End of Treatment and Follow-up Assessments o Section 6.1 Dose and Schedule of Docetaxel and Bevacizumab/Placebo o Section 7.2.2 Follow-up of Adverse Events o Appendix 15 Treatment and Assessment Schedule for Optional Post-Study Phase • Reason for Change: Instructions were added to clarify how adverse events should be reported following approval of Protocol Amendment H or site closure. o All clinical adverse events (AE) encountered during the clinical study will be reported on the AE form of the eCRF. Intensity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (see Appendix 8) and reported in detail as indicated on the eCRF. If an adverse event occurs which is not contained in the CTC AE v3.0, the five-point scale below will be used. Any treatment-related AEs occurring after approval of the Protocol Amendment H or site closure should be reported through the commercial spontaneous AEs reporting system.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported