Clinical trial results:
A MULTICENTER, PHASE III, RANDOMIZED, PLACEBO-CONTROLLED TRIAL EVALUATING THE EFFICACY AND SAFETY OF BEVACIZUMAB IN COMBINATION WITH CHEMOTHERAPY REGIMENS IN SUBJECTS WITH PREVIOUSLY UNTREATED METASTATIC BREAST CANCER

Summary

EudraCT number	2006-000378-61
Trial protocol	ES GB NL SE GR
Global end of trial date	08 January 2015

Results information

Result version number	v1 (current)
This version publication date	27 November 2016
First version publication date	27 November 2016

Trial information

Trial identification

Sponsor protocol code	AVF3694g

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00262067
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	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La 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 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the clinical benefit of the addition of bevacizumab to standard chemotherapy regimens (taxane or anthracycline based and capecitabine) for previously untreated metastatic breast cancer, as measured by progression-free survival based on investigator tumor assessment.

Protection of trial subjects:

Participants were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the participant and considering the local culture. The participants were provided an emergency medical call center help desk in the case of emergency during the study to ensure the safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 610
Country: Number of subjects enrolled	Ukraine: 82
Country: Number of subjects enrolled	Australia: 55
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 31
Country: Number of subjects enrolled	Philippines: 25
Country: Number of subjects enrolled	Brazil: 35
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	Singapore: 26
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	Panama: 4
Country: Number of subjects enrolled	Russian Federation: 126
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	United Kingdom: 42
Country: Number of subjects enrolled	France: 60

Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Guatemala: 20
Country: Number of subjects enrolled	Uruguay: 6
Country: Number of subjects enrolled	Peru: 5
Country: Number of subjects enrolled	Greece: 4
Worldwide total number of subjects	1237
EEA total number of subjects	161

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)	960
From 65 to 84 years	277
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 15 December 2005 to 8 January 2015 in the United States, Europe, and the rest of the world.

Pre-assignment

Screening details:

A total of 1237 participants were enrolled in the United States, Europe, and the rest of the world. Eligible participants were randomized in a 2:1 ratio to receive either chemotherapy plus bevacizumab or chemotherapy plus placebo.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bevacizumab + Taxane or Anthracycline

Arm description:

Eligible participants were administered Avastin® (bevacizumab) 15 milligrams (mg)/kilogram (kg) intravenously (IV) on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was packaged in either 5 milliliter (mL) (100 mg) or 20 mL (400 mg) glass vials containing 4 mL or 16 mL of bevacizumab, respectively (25 mg/mL for either vial).

Arm title	Placebo + Taxane or Anthracycline

Arm description:

Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was a clear to slightly opalescent and sterile liquid ready for intravenous administration.

Arm title	Bevacizumab + Capecitabine

Arm description:

Eligible participants were administered bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle +

capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was packaged in either 5 mL (100 mg) or 20 mL (400 mg) glass vials containing 4 mL or 16 mL of bevacizumab, respectively (25 mg/mL for either vial).

Arm title	Placebo + Capecitabine

Arm description:

Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was a clear to slightly opalescent and sterile liquid ready for intravenous administration.

Number of subjects in period 1	Bevacizumab + Taxane or Anthracycline	Placebo + Taxane or Anthracycline	Bevacizumab + Capecitabine
Started	415	207	409
Completed	0	0	0
Not completed	415	207	409
Physician decision	46	12	17
Consent withdrawn by subject	45	14	25
Disease progression	187	146	245
>60 days since last administration of BV	6	-	-
> 60 days since last administration of BV	-	1	8
Death	14	7	11
Other	12	6	5
Treatment completion	-	-	1
Adverse event	63	10	37
Lost to follow-up	-	3	-
Not known to have discontinued protocol therapy	36	7	55
Not treated	6	1	5

Number of subjects in period 1	Placebo +

	Capecitabine
Started	206
Completed	0
Not completed	206
Physician decision	6
Consent withdrawn by subject	5
Disease progression	145
>60 days since last administration of BV	-
> 60 days since last administration of BV	1
Death	6
Other	5
Treatment completion	-
Adverse event	11
Lost to follow-up	-
Not known to have discontinued protocol therapy	22
Not treated	5

Baseline characteristics

Reporting groups	
Reporting group title	Bevacizumab + Taxane or Anthracycline
Reporting group description:	
Eligible participants were administered Avastin® (bevacizumab) 15 milligrams (mg)/kilogram (kg) intravenously (IV) on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.	
Reporting group title	Placebo + Taxane or Anthracycline
Reporting group description:	
Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.	
Reporting group title	Bevacizumab + Capecitabine
Reporting group description:	
Eligible participants were administered bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.	
Reporting group title	Placebo + Capecitabine
Reporting group description:	
Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.	

Reporting group values	Bevacizumab + Taxane or Anthracycline	Placebo + Taxane or Anthracycline	Bevacizumab + Capecitabine
Number of subjects	415	207	409
Age categorical Units: Subjects			
< 40 years	29	14	21
40-64 years	295	160	289
≥ 65 years	91	33	99
Gender categorical Units: Subjects			
Female	413	207	408
Male	2	0	1

Reporting group values	Placebo + Capecitabine	Total	
Number of subjects	206	1237	
Age categorical Units: Subjects			
< 40 years	15	79	
40-64 years	137	881	
≥ 65 years	54	277	
Gender categorical Units: Subjects			
Female	204	1232	
Male	2	5	

End points

End points reporting groups

Reporting group title	Bevacizumab + Taxane or Anthracycline

Reporting group description:

Eligible participants were administered Avastin® (bevacizumab) 15 milligrams (mg)/kilogram (kg) intravenously (IV) on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Reporting group title	Placebo + Taxane or Anthracycline

Reporting group description:

Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Reporting group title	Bevacizumab + Capecitabine

Reporting group description:

Eligible participants were administered bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Reporting group title	Placebo + Capecitabine

Reporting group description:

Eligible participants were administered bevacizumab matching placebo IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Subject analysis set title	Intent-to-treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intent-to-treat (ITT) population included all participants who were randomized, regardless of whether they received any study medication or completed the full course of treatment.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population included all randomized participants who received any study treatment (at least one full or partial dose of either study medication or chemotherapy).

Primary: Progression-free Survival as Determined by the Investigator Using Response Evaluation Criteria in Solid Tumors

End point title	Progression-free Survival as Determined by the Investigator Using Response Evaluation Criteria in Solid Tumors

End point description:

Progression-free Survival (PFS) was defined as time from randomization to first documented disease progression (PD). It was determined by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 or death due to any cause, whichever occurred first. For target lesions, PD was defined as at least 20% increase in sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or appearance of one or more new lesions. For non-target lesions, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. ITT population was considered for this end point.

End point type	Primary

End point timeframe:

From first participant in (15 December 2005) till PFS analysis cut-off (31 July 2008) (Up to 2 years, 7 months)

End point values	Bevacizumab + Taxane or Anthracycline	Placebo + Taxane or Anthracycline	Bevacizumab + Capecitabine	Placebo + Capecitabine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	415	207	409	206
Units: Months				
median (confidence interval 95%)	9.2 (8.6 to 10.1)	8 (6.7 to 8.4)	8.6 (8.1 to 9.5)	5.7 (4.3 to 6.2)

Statistical analyses

Statistical analysis title	T/Anth+Placebo VS T/Anth+BV
Comparison groups	Bevacizumab + Taxane or Anthracycline v Placebo + Taxane or Anthracycline
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.644
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.522
upper limit	0.795

Statistical analysis title	Cap+Placebo VS Cap+BV
Comparison groups	Bevacizumab + Capecitabine v Placebo + Capecitabine
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.564
upper limit	0.84

Secondary: Objective Response Rate as Assessed by Investigator Using RECIST

End point title	Objective Response Rate as Assessed by Investigator Using RECIST

End point description:

An objective response was defined as a complete response or a partial response determined on two consecutive occasions >= 4 weeks apart as determined by the investigator using RECIST 1.0. Objective response rate (ORR) was defined as the percentage of participants who had an objective response. For target lesions, a complete response was defined as the disappearance of all target lesions and 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. For non-target lesions, a complete response was defined as the disappearance of all non-target lesions and a partial response was defined as the persistence of one or more non-target lesions. Analysis population consisted of randomized participants (ITT population) who had measurable disease at baseline.

End point type	Secondary

End point timeframe:

From first participant in (15 December 2005) till ORR analysis cut-off (31 July 2008) (Up to 2 years, 7 months)

End point values	Bevacizumab + Taxane or Anthracycline	Placebo + Taxane or Anthracycline	Bevacizumab + Capecitabine	Placebo + Capecitabine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	345[1]	177[2]	325[3]	161[4]
Units: Percentage of participants				
number (confidence interval 95%)	51.3 (45.9 to 56.7)	37.9 (30.7 to 45.2)	35.4 (30.2 to 40.6)	23.6 (17.6 to 30.7)

Notes:

[1] - Only participants with measurable disease at baseline were included in the analysis.

[2] - Only participants with measurable disease at baseline were included in the analysis.

[3] - Only participants with measurable disease at baseline were included in the analysis.

[4] - Only participants with measurable disease at baseline were included in the analysis.

Statistical analyses

Statistical analysis title	T/Anth+Placebo vs T/Anth+BV
Comparison groups	Placebo + Taxane or Anthracycline v Bevacizumab + Taxane or Anthracycline
Number of subjects included in analysis	522
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0054
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference in ORR
Point estimate	13.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	22.3

Statistical analysis title	Cap+Placebo VS Cap+BV
Comparison groups	Bevacizumab + Capecitabine v Placebo + Capecitabine

Number of subjects included in analysis	486
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0097
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage difference in ORR
Point estimate	11.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	20.2

Secondary: Duration of Objective Response as Determined by the Investigator Using RECIST

End point title	Duration of Objective Response as Determined by the Investigator Using RECIST

End point description:

Duration of objective response was defined as the time from the first tumor assessment that led to a determination of an objective response to the time of disease progression or death due to any cause, whichever occurred first. Analysis population consisted of randomized participants (ITT population) who had measurable disease at baseline and achieved an objective response.

End point type	Secondary

End point timeframe:

From first participant in (15 December 2005) till objective response analysis cut-off (31 July 2008) (Up to 2 years, 7 months)

End point values	Bevacizumab + Taxane or Anthracycline	Placebo + Taxane or Anthracycline	Bevacizumab + Capecitabine	Placebo + Capecitabine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	177[5]	67[6]	115[7]	38[8]
Units: Months				
median (confidence interval 95%)	8.3 (7.2 to 10.7)	7.1 (6.2 to 8.8)	9.2 (8.5 to 10.4)	7.2 (5.1 to 9.3)

Notes:

[5] - Only participants with measurable disease at baseline and who had objective response were included.
[6] - Only participants with measurable disease at baseline and who had objective response were included.
[7] - Only participants with measurable disease at baseline and who had objective response were included.
[8] - Only participants with measurable disease at baseline and who had objective response were included.

Statistical analyses

Statistical analysis title	T/Anth+Placebo VS T/Anth+BV
Comparison groups	Bevacizumab + Taxane or Anthracycline v Placebo + Taxane or Anthracycline

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0064
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.627
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.447
upper limit	0.88

Statistical analysis title	Cap+Placebo VS Cap+BV
Comparison groups	Bevacizumab + Capecitabine v Placebo + Capecitabine
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0326
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.612
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.388
upper limit	0.964

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from randomization until death from any cause. ITT population was considered for this end point. The median value and value of upper limit of confidence interval for Placebo + Taxane or Anthracycline was 'not reached' and 'not estimable', respectively. However, the EudraCT portal does not accept blank field or have free text option for the explanation; therefore, we have presented an arbitrary value (99999) for the same.

End point type	Secondary

End point timeframe:

From first participant in (15 December 2005) till overall survival analysis cut-off (24 February 2009) (Up to 3 years, 2 months)

End point values	Bevacizumab + Taxane or Anthracycline	Placebo + Taxane or Anthracycline	Bevacizumab + Capecitabine	Placebo + Capecitabine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	415	207	409	206
Units: Months				
median (confidence interval 95%)	27.5 (25.6 to 31.4)	99999 (23.6 to 99999)	25.7 (22 to 28.4)	22.8 (20.5 to 28.4)

Statistical analyses

Statistical analysis title	T/Anth+Placebo VS T/Anth+BV
Comparison groups	Bevacizumab + Taxane or Anthracycline v Placebo + Taxane or Anthracycline
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.44
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.43

Statistical analysis title	Cap+Placebo VS Cap+BV
Comparison groups	Bevacizumab + Capecitabine v Placebo + Capecitabine
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.33
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.13

Secondary: One-year Survival Rate

End point title	One-year Survival Rate

End point description:

One-year survival rate was defined as the percentage of participants who were alive one-year after randomization. The percentage of participants alive at one-year was determined using Kaplan-Meier analyses and the 95% confidence intervals were computed using the Greenwood's formula. ITT population was considered for this end point.

End point type	Secondary

End point timeframe:

One year after randomization for each participant

End point values	Bevacizumab + Taxane or Anthracycline	Placebo + Taxane or Anthracycline	Bevacizumab + Capecitabine	Placebo + Capecitabine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	415	207	409	206
Units: Percentage of participants				
number (confidence interval 95%)	80.7 (76.8 to 84.5)	83.2 (78.1 to 88.4)	81 (77.1 to 84.8)	74.8 (68.7 to 80.8)

Statistical analyses

Statistical analysis title	T/Anth+Placebo vs T/Anth+BV
Comparison groups	Bevacizumab + Taxane or Anthracycline v Placebo + Taxane or Anthracycline
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.436
Method	Normal approximation
Parameter estimate	% difference in one−year survival rate
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	3.9

Statistical analysis title	Cap+Placebo VS Cap+BV
Comparison groups	Bevacizumab + Capecitabine v Placebo + Capecitabine
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.092
Method	Normal approximation
Parameter estimate	% difference in one−year survival rate
Point estimate	6.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	13.4

Secondary: PFS as Determined by the Independent Review Committee Using RECIST

End point title	PFS as Determined by the Independent Review Committee Using RECIST

End point description:

PFS was defined as time from randomization to first documented PD. It was determined by independent review committee using RECIST 1.0 or death due to any cause, whichever occurred first. For target lesions, PD was defined as at least 20% increase in sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or appearance of one or more new lesions. For non-target lesions, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. ITT population was considered for this end point.

End point type	Secondary

End point timeframe:

From first participant in (15 December 2005) till PFS analysis cut-off (31 July 2008) (Up to 2 years, 7 months)

End point values	Bevacizumab + Taxane or Anthracycline	Placebo + Taxane or Anthracycline	Bevacizumab + Capecitabine	Placebo + Capecitabine
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	415	207	409	206
Units: Months				
median (confidence interval 95%)	10.7 (9.9 to 12.1)	8.3 (8 to 9.9)	9.8 (8.4 to 10.4)	6.2 (4.7 to 7.8)

Statistical analyses

Statistical analysis title	T/Anth+Placebo VS T/Anth+BV
Comparison groups	Bevacizumab + Taxane or Anthracycline v Placebo + Taxane or Anthracycline
Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.601
upper limit	0.988

Statistical analysis title	Cap+Placebo VS Cap+BV
Comparison groups	Bevacizumab + Capecitabine v Placebo + Capecitabine
Number of subjects included in analysis	615
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0011
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.681
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.858

Secondary: Number of Participants With Serious Adverse Events after final overall survival analysis (24 February 2009) till end of study (8 January 2015)

End point title	Number of Participants With Serious Adverse Events after final overall survival analysis (24 February 2009) till end of study (8 January 2015)

End point description:

A serious adverse event (SAE) is any untoward medical occurrence that at any dose results in death, is life threatening, requires hospitalization or prolongation of hospitalization or results in disability/incapacity, and congenital anomaly/birth defect. The SAEs presented here were collected from 24 February 2009 to 8 January 2015. Safety population was considered for this end point.

End point type	Secondary

End point timeframe:

Post final overall survival analysis (24 February 2009) till end of study (8 January 2015) (Approximately 6 years)

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	1220			
Units: Number	21			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 3 years, 2 months (First participant enrolment [15 December 2005] to data cut-off date [24 February 2009])

Adverse event reporting additional description:

Adverse event is reported for safety population which included all randomized participants who received any study treatment, defined as at least one full or partial dose of either study drug or chemotherapy.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Bevacizumab + Taxane or Anthracycline

Reporting group description:

Participants received bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Reporting group title	Placebo + Taxane or Anthracycline

Reporting group description:

Participants received bevacizumab matching placebo IV on Day 1 of every 21-day cycle + either a taxane or anthracycline (minimum 6 cycles and maximum 8 cycles of anthracycline)-based standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Reporting group title	Bevacizumab + Capecitabine

Reporting group description:

Participants received bevacizumab 15 mg/kg IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Reporting group title	Placebo + Capecitabine

Reporting group description:

Participants received bevacizumab matching placebo IV on Day 1 of every 21-day cycle + capecitabine standard chemotherapy for metastatic breast cancer until disease progression, treatment-limiting toxicity, or death due to any cause.

Serious adverse events	Bevacizumab + Taxane or Anthracycline	Placebo + Taxane or Anthracycline	Bevacizumab + Capecitabine
Total subjects affected by serious adverse events			
subjects affected / exposed	146 / 413 (35.35%)	57 / 202 (28.22%)	132 / 404 (32.67%)
number of deaths (all causes)	18	9	15
number of deaths resulting from adverse events	6	4	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Breast cancer metastatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastases to meninges			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour ulceration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Metastatic neoplasm			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
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 cancer			

subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Vascular disorders			
Deep vein thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	1 / 202 (0.50%)	3 / 404 (0.74%)
occurrences causally related to treatment / all	1 / 2	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 413 (1.21%)	0 / 202 (0.00%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	6 / 6	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 413 (0.73%)	1 / 202 (0.50%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Malaise			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	6 / 404 (1.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 413 (0.73%)	2 / 202 (0.99%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	1 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 413 (0.97%)	1 / 202 (0.50%)	7 / 404 (1.73%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Immune system disorders			
Hypersensitivity			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Reproductive system and breast disorders			
Metrorrhagia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Uterine haemorrhage			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Asthma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Chronic obstructive pulmonary disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Diaphragmatic hernia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
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			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 413 (1.21%)	2 / 202 (0.99%)	6 / 404 (1.49%)
occurrences causally related to treatment / all	0 / 6	0 / 3	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea exertional			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	1 / 202 (0.50%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pleural effusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 413 (1.21%)	3 / 202 (1.49%)	5 / 404 (1.24%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pleuritic pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Pneumonia aspiration			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Pneumothorax			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	1 / 202 (0.50%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 0

Pulmonary embolism			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 413 (0.73%)	3 / 202 (1.49%)	8 / 404 (1.98%)
occurrences causally related to treatment / all	3 / 3	2 / 3	6 / 8
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Pulmonary haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Respiratory arrest			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Respiratory failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Tracheomalacia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Psychiatric disorders			
Anxiety			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Completed suicide			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Confusional state			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	3 / 404 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Mental status changes			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	1 / 202 (0.50%)	3 / 404 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood potassium increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Haemoglobin decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus test positive			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
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 physical condition abnormal			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Injury, poisoning and procedural complications			
Ankle fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Cervical vertebral fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug toxicity			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femoral neck fracture alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Fibula fracture alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	3 / 404 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Procedural pain alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Radiation oesophagitis alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Spinal compression fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
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 limb fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
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			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Femur fracture			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Angina pectoris			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Cardiac arrest			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	2 / 413 (0.48%)	1 / 202 (0.50%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 413 (0.24%)	2 / 202 (0.99%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiomyopathy			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracardiac thrombus			

subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Left ventricular dysfunction			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Myocardial infarction			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	6 / 404 (1.49%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pericardial effusion			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Restrictive cardiomyopathy			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinus arrest			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			

subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Ventricular dysfunction			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac valve disease			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Coronary artery disease			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Carotid sinus syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma hepatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Convulsion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Facial palsy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 413 (0.73%)	1 / 202 (0.50%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	0 / 404 (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
Neuralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Peripheral motor neuropathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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 sensory neuropathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	0 / 404 (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
Reversible posterior leukoencephalopathy syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Somnolence			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Syncope			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 413 (0.73%)	1 / 202 (0.50%)	3 / 404 (0.74%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphasia			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 413 (0.73%)	0 / 202 (0.00%)	3 / 404 (0.74%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	26 / 413 (6.30%)	11 / 202 (5.45%)	3 / 404 (0.74%)
occurrences causally related to treatment / all	2 / 29	0 / 11	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	10 / 413 (2.42%)	5 / 202 (2.48%)	3 / 404 (0.74%)
occurrences causally related to treatment / all	2 / 15	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Eye disorders			
Blindness			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 413 (0.97%)	1 / 202 (0.50%)	4 / 404 (0.99%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Colitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 413 (1.94%)	0 / 202 (0.00%)	6 / 404 (1.49%)
occurrences causally related to treatment / all	2 / 8	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Duodenal ulcer haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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

Faecaloma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 413 (1.21%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	4 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Gastrointestinal toxicity			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal ulcer perforation			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Ileus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Intestinal perforation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Jejunitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	0 / 404 (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
Nausea			
alternative assessment type: Non-systematic			

subjects affected / exposed	6 / 413 (1.45%)	1 / 202 (0.50%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	0 / 9	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Pancreatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Small intestinal haemorrhage			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Small intestinal obstruction			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Upper gastrointestinal haemorrhage			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 413 (1.45%)	3 / 202 (1.49%)	4 / 404 (0.99%)
occurrences causally related to treatment / all	2 / 7	0 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Cholelithiasis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic function abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatorenal failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Hyperbilirubinaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
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			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain of skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmar−plantar erythrodysaesthesia syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Renal and urinary disorders			
Calculus ureteric			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Nephrotic syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
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 acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 413 (0.73%)	1 / 202 (0.50%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Urinary retention			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Back pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 413 (0.24%)	1 / 202 (0.50%)	5 / 404 (1.24%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	1 / 202 (0.50%)	0 / 404 (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
Neck pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal deformity			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Abscess intestinal			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Abscess jaw			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Bacteraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Breast cellulitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Bronchitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchopneumonia alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Catheter related infection alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	3 / 404 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 413 (1.69%)	1 / 202 (0.50%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	1 / 8	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central line infection alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Cystitis alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	1 / 202 (0.50%)	0 / 404 (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
Diverticulitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes oesophagitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 413 (0.97%)	1 / 202 (0.50%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 5	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lobar pneumonia alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Lower respiratory tract infection alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Neutropenic sepsis alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	2 / 202 (0.99%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Osteomyelitis alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Pneumonia alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 413 (0.73%)	5 / 202 (2.48%)	6 / 404 (1.49%)
occurrences causally related to treatment / all	1 / 3	0 / 5	0 / 6
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Salpingo-oophoritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 413 (1.45%)	1 / 202 (0.50%)	3 / 404 (0.74%)
occurrences causally related to treatment / all	2 / 7	0 / 1	0 / 3
deaths causally related to treatment / all	1 / 2	0 / 1	0 / 1
Sinusitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Staphylococcal bacteraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Sweat gland infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	2 / 202 (0.99%)	2 / 404 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Wound infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
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 / 413 (0.24%)	0 / 202 (0.00%)	0 / 404 (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
Urosepsis			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 413 (1.69%)	1 / 202 (0.50%)	5 / 404 (1.24%)
occurrences causally related to treatment / all	0 / 7	0 / 1	0 / 7
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fluid overload			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	0 / 404 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 413 (0.00%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 413 (0.48%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorexia			
subjects affected / exposed	1 / 413 (0.24%)	0 / 202 (0.00%)	1 / 404 (0.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo + Capecitabine		
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 201 (31.84%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Breast cancer metastatic			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to meninges				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 201 (1.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Tumour pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour ulceration				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic neoplasm				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric cancer				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Malignant pleural effusion				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cancer				

subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 201 (1.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jugular vein thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicose vein			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis limb				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 201 (1.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	3 / 201 (1.49%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Fatigue				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malaise			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mucosal inflammation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 201 (1.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sudden death			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Metrorrhagia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uterine haemorrhage				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Asthma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cough				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diaphragmatic hernia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 201 (1.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypoxia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Lung infiltration				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
alternative assessment type: Non-systematic				
subjects affected / exposed	5 / 201 (2.49%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 1			
Pleuritic pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
alternative assessment type: Non-systematic				

subjects affected / exposed	5 / 201 (2.49%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	2 / 2			
Pulmonary haemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory arrest				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tracheomalacia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Completed suicide				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Confusional state				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood potassium increased				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rotavirus test positive				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical condition abnormal				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Concussion				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug toxicity				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Femoral neck fracture alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fibula fracture alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Head injury alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Overdose alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Procedural pain alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radiation oesophagitis alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound dehiscence				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				

subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial tachycardia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiogenic shock				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiomyopathy				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intracardiac thrombus				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Left ventricular failure				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	2 / 201 (1.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Restrictive cardiomyopathy				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus arrest				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular dysfunction				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac valve disease				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ataxia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carotid sinus syndrome				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
alternative assessment type: Non-systematic				

subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cerebrovascular accident				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Coma hepatic				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Convulsion				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Facial palsy				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lethargy				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Nervous system disorder				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral motor neuropathy				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reversible posterior leukoencephalopathy syndrome				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sciatica				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Somnolence				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphasia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile bone marrow aplasia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				

subjects affected / exposed	3 / 201 (1.49%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Iron deficiency anaemia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	2 / 201 (1.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Blindness				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Macular hole				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 201 (1.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 201 (1.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer haemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Faecaloma				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis erosive				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal perforation				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal toxicity				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haemorrhoids				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileal ulcer perforation				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jejunitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
alternative assessment type: Non-systematic				
subjects affected / exposed	3 / 201 (1.49%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic cirrhosis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic function abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 201 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatorenal failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaundice cholestatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pain of skin				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palmar−plantar erythrodysaesthesia syndrome				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin ulcer				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Calculus ureteric				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephrotic syndrome				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ureteric obstruction				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Hypercalcaemia of malignancy				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back pain				
alternative assessment type: Non-systematic				

subjects affected / exposed	2 / 201 (1.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Bone pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neck pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal deformity				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal abscess				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abscess intestinal				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abscess jaw				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Breast cellulitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Bronchopneumonia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Catheter related infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 201 (1.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Central line infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridial infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 201 (1.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes oesophagitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Klebsiella bacteraemia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Lobar pneumonia alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nasopharyngitis alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngitis alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia alternative assessment type: Non-systematic				

subjects affected / exposed	4 / 201 (1.99%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Salpingo-oophoritis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sweat gland infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Wound infection				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 201 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fluid overload				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 201 (0.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
alternative assessment type: Non-systematic				

subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anorexia			
subjects affected / exposed	0 / 201 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bevacizumab + Taxane or Anthracycline	Placebo + Taxane or Anthracycline	Bevacizumab + Capecitabine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 413 (23.24%)	28 / 202 (13.86%)	80 / 404 (19.80%)
Vascular disorders			
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	43 / 413 (10.41%)	8 / 202 (3.96%)	51 / 404 (12.62%)
occurrences (all)	122	14	149
Cardiac disorders			
Left ventricular dysfunction			
alternative assessment type: Non-systematic			
subjects affected / exposed	19 / 413 (4.60%)	8 / 202 (3.96%)	3 / 404 (0.74%)
occurrences (all)	53	17	6
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	21 / 413 (5.08%)	10 / 202 (4.95%)	18 / 404 (4.46%)
occurrences (all)	49	26	37
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	25 / 413 (6.05%)	6 / 202 (2.97%)	18 / 404 (4.46%)
occurrences (all)	137	13	59

Non-serious adverse events	Placebo + Capecitabine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 201 (9.95%)		
Vascular disorders			
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 201 (3.98%)		
occurrences (all)	11		
Cardiac disorders			
Left ventricular dysfunction			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 201 (1.00%)		
occurrences (all)	7		
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 201 (2.49%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	5 / 201 (2.49%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2006	Study AVF3694g was amended to provide more clarity and rigorous guidelines for study therapy in both the blinded treatment and post-progression phases. Safety information was also updated to be consistent with current standard bevacizumab dose modification guidelines. Protocol-specified selected adverse events and special reporting for nonserious cardiac adverse events were further defined. For this study, all intracranial hemorrhages were reported as serious and were therefore subject to serious adverse event reporting requirements. Safety monitoring of left ventricular function during initial screening was added for subjects with prior exposure to anthracycline-based therapy, rather than only for subjects entering the anthracycline cohort. All Grade >= 2 left ventricular systolic dysfunction events were reported immediately to the Sponsor to allow for a timely and thorough review of cardiotoxicity events by the Data Monitoring Committee.
22 November 2006	Study AVF3694g was amended to better fit the practice patterns of oncologists treating first-line metastatic breast cancer with chemotherapy. Major changes to the protocol are described below: • Secondary objectives and outcome measures were amended to include 1-year survival. • Modifications were made to the exclusion criteria, including allowing subjects who had unknown HER2 status and for whom the determination of HER2 status was not possible and disallowing subjects who had received radiotherapy within 2 weeks prior to Day 0. • Subjects with a history of anaphylactic reaction to monoclonal antibody therapy not controlled with treatment premedication were excluded from receiving bevacizumab. • Optional unblinding was allowed when a subject had documented progressive disease and if such information was instrumental in determining the next course of treatment. • For subjects who received prior anthracycline therapy or who were to be enrolled to the anthracycline cohort, an echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan was required (may be performed within 12 weeks prior to Day 0 if no cardiotoxic treatments or events occur within that period). Subjects who were to be enrolled into the anthracycline cohort should have had left ventricular ejection fraction (LVEF) >= 50%. Subjects who had received prior anthracycline therapy and were to be enrolled into the taxane or capecitabine cohort could not have New York Heart Association (NYHA) Grade II or higher CHF. • Subjects who had alkaline phosphatase > 2× the upper limit of normal (ULN; > 7× ULN in subjects with known bone involvement) were excluded from study entry.
20 February 2007	Study AVF3694g was amended to detect, statistically, the clinical benefit of the addition of bevacizumab to capecitabine therapy compared with capecitabine alone for first-line metastatic breast cancer participants. This study design allowed detection of the clinical benefit of the addition of bevacizumab to taxane therapy and anthracycline-based therapy in a parallel analysis.
24 July 2007	Study AVF3694g was amended to provide more information in support of the primary endpoint of progression free survival (PFS) and secondary endpoint of overall survival. An Independent Review Committee (IRC) assessment was added to meet study design guidelines and provide a sensitivity analysis for the investigator assessment−based primary endpoint. Additional subsequent anti-cancer therapy during the survival follow-up phase for all subjects were captured to provide information on therapies that may contribute to overall survival of participants after they had discontinued from the blinded phase of the study. The definition of PFS was updated, to be well characterized and accepted by the regulatory and research communities.

27 March 2008	Study AVF3694g was amended to provide bevacizumab in an optional extended treatment phase to all subjects receiving study treatment when the study analysis was complete if the primary efficacy analysis showed significant improvement with bevacizumab without a detrimental effect on subject safety. The maximum duration of treatment with bevacizumab (blinded treatment phase plus optional open-label post-progression phase and/or extended treatment phase) was increased to 48 months; this allowed subjects who were benefiting from bevacizumab treatment to continue to receive it.
12 May 2011	Study AVF3694g was amended to remove the maximum duration of treatment with bevacizumab (blinded treatment phase plus optional open-label post-progression phase and/or extended treatment phase) to all participants receiving study treatment when the study analysis was complete, if the primary efficacy analysis shows significant improvement with bevacizumab without a detrimental effect on subject safety. This was allow participants who are benefiting from bevacizumab treatment to continue to receive it. Other significant changes to the protocol has been described below: • Study treatment information and the study assessment schedule have been updated to reflect the amended duration of treatment of the optional extended treatment phase. • Only serious adverse event data was continue to be collected and reported as currently required by the protocol. Participants who were no longer receiving bevacizumab through the study have completed the study, and no further data need to be recorded. • Bevacizumab safety information was updated. • The sample Informed Consent Form was revised to reflect the changes to the protocol and the updated risk section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported