Clinical trial results:
A Multicenter Phase III Randomized Trial of Adjuvant Therapy for Patients With HER2-Positive Node-Positive or High Risk Node-Negative Breast Cancer Comparing Chemotherapy Plus Trastuzumab With Chemotherapy Plus Trastuzumab Plus Bevacizumab

Summary

EudraCT number	2007-005182-35
Trial protocol	DE FR GB IE LV ES BE AT SK CZ HU PT EE SE SI IT BG GR
Global end of trial date	17 April 2014

Results information

Result version number	v1 (current)
This version publication date	05 February 2016
First version publication date	05 February 2016

Trial information

Trial identification

Sponsor protocol code	BO20906

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00625898
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 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, 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	10 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This is an international, multi-center, open-label, randomized Phase III trial of adjuvant therapy for participants with HER2-positive node-positive or high risk node-negative breast cancer to determine whether the addition of bevacizumab of two designated regimens of chemotherapy plus trastuzumab (TCHBHB; THBFECHB) improves efficacy and safety of two designated regimen of chemotherapy plus trastuzumab (TCHH; THFECH). TCHBHB = docetaxel (T), carboplatin (C), trastuzumab (H), bevacizumab (B) followed by trastuzumab (T) and bevacizumab (B). THBFECHB = THB followed by 5-fluorouracil (F), epirubicin (E), and cyclophosphamide (C) followed by HB. TCHH = TCH followed by H. THFECH = TH followed by FEC followed by H.

Protection of trial subjects:

Study BO20906 was conducted in accordance with the principles of the Declaration of Helsinki, and in accordance with the protocol, Good Clinical Practice Guidelines, and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Australia: 76
Country: Number of subjects enrolled	Bosnia and Herzegovina: 25
Country: Number of subjects enrolled	Brazil: 79
Country: Number of subjects enrolled	Canada: 268
Country: Number of subjects enrolled	China: 147
Country: Number of subjects enrolled	Croatia: 19
Country: Number of subjects enrolled	Egypt: 12
Country: Number of subjects enrolled	Hong Kong: 15
Country: Number of subjects enrolled	Israel: 44
Country: Number of subjects enrolled	Korea, Republic of: 328
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Peru: 34
Country: Number of subjects enrolled	Philippines: 39
Country: Number of subjects enrolled	Romania: 31

Country: Number of subjects enrolled	Russian Federation: 82
Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	South Africa: 19
Country: Number of subjects enrolled	Taiwan: 48
Country: Number of subjects enrolled	Thailand: 28
Country: Number of subjects enrolled	United States: 984
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Ireland: 41
Country: Number of subjects enrolled	Italy: 117
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Poland: 138
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Slovenia: 3
Country: Number of subjects enrolled	Spain: 243
Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	United Kingdom: 55
Country: Number of subjects enrolled	Austria: 62
Country: Number of subjects enrolled	Belgium: 59
Country: Number of subjects enrolled	Bulgaria: 30
Country: Number of subjects enrolled	Estonia: 5
Country: Number of subjects enrolled	France: 127
Country: Number of subjects enrolled	Germany: 274
Worldwide total number of subjects	3509
EEA total number of subjects	1251

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)	3199
From 65 to 84 years	310
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Prior to the screening evaluation, participants were informed of the nature of the study drug, intended purpose, possible benefits, and possible adverse experiences. Participants were screened by central testing for resected node-positive or high risk node-negative invasive breast cancer HER2-positive and randomized.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Chemotherapy + Trastuzumab

Arm description:

Non-anthracycline based regimen (Group 1A TCHH): participants received 6 cycles of docetaxel 75 milligrams per square meter (mg/m^2) intravenously (IV) along with carboplatin 6 milligrams per milliliter per minute (mg/mL/min) area under the curve (AUC) IV, every three weeks (q3w) plus (+) trastuzumab (first dose: 8 milligrams per kilogram [mg/kg] IV and then 6 mg/kg IV) followed by trastuzumab alone (6 mg/kg) every 3 weeks to complete one year of therapy.
Anthracycline based regimen (Group 2A: THFECH): participants received 3 cycles q3w of trastuzumab (first dose: 8 mg/kg Cycle 1 and 6 mg/kg Doses 2 and 3) and docetaxel 100 mg/m^2 IV followed by 3 cycles q3w of 5-Fluorouracil (5-FU) 600 mg/m^2 IV push; epirubicin 90 mg/m^2 IV; cyclophosphamide 600 mg/m^2 IV and then trastuzumab alone (Dose 4: 8 mg/kg Cycle 1 and then 6 mg/kg) q3w to complete one year of therapy.

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants in non-Anthracycline based regimen (TCHH) received 75 mg/m^2 docetaxel IV over 60 minutes, q3w for 6 cycles. Participants in anthracycline based regimen (THFECH) received 100 mg/m^2 docetaxelIV over 60 minutes, q3w for 3 cycles.

Investigational medicinal product name	5-Fluorouracil (5-FU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants in Anthracycline based regimen(THFECH) received 600 mg/m^2 IV push 5-FU, q3w for 3 cycles.

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

Dosage and administration details:

Participants in non-anthracycline based regimen (TCHH) received AUC 6 mg/mL/min IV carboplatin over 30 to 60 minutes, q3w for 6 cycles.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received trastuzumab (first dose: 8 mg/kg IV and then 6 mg/kg) IV q3w to complete one year of therapy in non-anthracycline based regimen (TCHH). In anthracycline based regimen (THFECH), participants received 3 cycles of trastuzumab (first dose: 8 mg/kg Cycle 1 and 6 mg/kg Doses 2 and 3) and then after the completion of FEC regimen, participant received trastuzumab (Dose 4: 8 mg/kg Cycle 1 and then 6 mg/kg) q3w to complete one year on therapy.

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

Dosage and administration details:

Participants in anthracycline based regimen (THFECH) received 90 mg/m^2 IV epirubicin, q3w for 3 cycles.

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

Dosage and administration details:

Participants in anthracycline based regimen (THFECH) received 600 mg/m^2 IV cyclophosphamide, q3w for 3 cycles.

Arm title	Chemotherapy + Trastuzumab + Bevacizumab

Arm description:

Non-anthracycline based regimen (Group 1B:TCHBHB): Participants received 6 cycles of docetaxel 75 mg/m^2 IV along with carboplatin 6 mg/mL/min AUC IV, q3w + trastuzumab (8 mg/kg IV in Cycle 1 and then 6 mg/kg IV) and bevacizumab (15 mg/kg IV) followed by trastuzumab (6 mg/kg) +bevacizumab (15 mg/kg IV) every 3 weeks to complete one year of therapy.
Anthracycline based regimen (Group 2B: THBFECHB): Participants received 3 cycles of q3w of trastuzumab (first dose: 8 mg/kg Cycle 1 and 6 mg/kg Doses 2 and 3), bevacizumab 15 mg/kg IV, and docetaxel 100 mg/m^2 IV followed by 3 cycles q3w of 5-FU 600 mg/m^2 IV push; epirubicin 90 mg/m^2 IV; cyclophosphamide 600 mg/m^2 IV and then trastuzumab (Dose 4: 8 mg/kg Cycle 1 and 6 mg/kg) and bevacizumab (15 mg/kg IV) every 3 weeks to complete one year of therapy.

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

Dosage and administration details:

Participants in non-Anthracycline based regimen (TCHH) received 75 mg/m^2 docetaxel IV over 60 minutes, q3w for 6 cycles. Participants in anthracycline based regimen (THFECH) received 100 mg/m^2 docetaxelIV over 60 minutes, q3w for 3 cycles.

Investigational medicinal product name	5-Fluorouracil (5-FU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants in Anthracycline based regimen(THFECH) received 600 mg/m^2 IV push 5-FU, q3w for 3 cycles.

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

Dosage and administration details:

Participants in non-anthracycline based regimen (TCHH) received AUC 6 mg/mL/min IV carboplatin over 30 to 60 minutes, q3w for 6 cycles.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received trastuzumab (first dose: 8 mg/kg IV and then 6 mg/kg) IV q3w to complete one year of therapy in non-anthracycline based regimen (TCHH). In anthracycline based regimen (THFECH), participants received 3 cycles of trastuzumab (first dose: 8 mg/kg Cycle 1 and 6 mg/kg Doses 2 and 3) and then after the completion of FEC regimen, participant received trastuzumab (Dose 4: 8 mg/kg Cycle 1 and then 6 mg/kg) q3w to complete one year on therapy.

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

Dosage and administration details:

Participants in anthracycline based regimen (THFECH) received 90 mg/m^2 IV epirubicin, q3w for 3 cycles.

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

Dosage and administration details:

Participants in anthracycline based regimen (THFECH) received 600 mg/m^2 IV cyclophosphamide, q3w for 3 cycles.

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

Dosage and administration details:

Participants received 15 mg/kg of bevacizumab IV q3w every 3 weeks to complete one year of therapy q3w for 17 cycles in non-anthracycline based regimen(TCHBHB). In anthracycline based regimen (THBFECHB), participants received 3 cycles of bevacizumab IV 15 mg/kg and then after the completion of FEC regimen, participants received bevacizumab IV 15 mg/kg every 3 weeks to complete one year on therapy.

Number of subjects in period 1	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab
Started	1757	1752
Treated	1740	1732
Assigned treatment received	1739	1721
Incorrect treatment received	1	11
Completed	0	0
Not completed	1757	1752
Participants died	78	70
Lost to follow-up	116	154
Alive in follow-up	1563	1528

Baseline characteristics

Reporting groups	
Reporting group title	Chemotherapy + Trastuzumab

Reporting group description:

Non-anthracycline based regimen (Group 1A TCHH): participants received 6 cycles of docetaxel 75 milligrams per square meter (mg/m^2) intravenously (IV) along with carboplatin 6 milligrams per milliliter per minute (mg/mL/min) area under the curve (AUC) IV, every three weeks (q3w) plus (+) trastuzumab (first dose: 8 milligrams per kilogram [mg/kg] IV and then 6 mg/kg IV) followed by trastuzumab alone (6 mg/kg) every 3 weeks to complete one year of therapy.
Anthracycline based regimen (Group 2A: THFECH): participants received 3 cycles q3w of trastuzumab (first dose: 8 mg/kg Cycle 1 and 6 mg/kg Doses 2 and 3) and docetaxel 100 mg/m^2 IV followed by 3 cycles q3w of 5-Fluorouracil (5-FU) 600 mg/m^2 IV push; epirubicin 90 mg/m^2 IV; cyclophosphamide 600 mg/m^2 IV and then trastuzumab alone (Dose 4: 8 mg/kg Cycle 1 and then 6 mg/kg) q3w to complete one year of therapy.

Reporting group title	Chemotherapy + Trastuzumab + Bevacizumab

Reporting group description:

Non-anthracycline based regimen (Group 1B:TCHBHB): Participants received 6 cycles of docetaxel 75 mg/m^2 IV along with carboplatin 6 mg/mL/min AUC IV, q3w + trastuzumab (8 mg/kg IV in Cycle 1 and then 6 mg/kg IV) and bevacizumab (15 mg/kg IV) followed by trastuzumab (6 mg/kg) +bevacizumab (15 mg/kg IV) every 3 weeks to complete one year of therapy.
Anthracycline based regimen (Group 2B: THBFECHB): Participants received 3 cycles of q3w of trastuzumab (first dose: 8 mg/kg Cycle 1 and 6 mg/kg Doses 2 and 3), bevacizumab 15 mg/kg IV, and docetaxel 100 mg/m^2 IV followed by 3 cycles q3w of 5-FU 600 mg/m^2 IV push; epirubicin 90 mg/m^2 IV; cyclophosphamide 600 mg/m^2 IV and then trastuzumab (Dose 4: 8 mg/kg Cycle 1 and 6 mg/kg) and bevacizumab (15 mg/kg IV) every 3 weeks to complete one year of therapy.

Reporting group values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab	Total
Number of subjects	1757	1752	3509
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	50.7	50.8	
standard deviation	± 10	± 10.25	-
Gender categorical Units: Subjects			
Female	1757	1752	3509
Male	0	0	0

End points

End points reporting groups

Reporting group title	Chemotherapy + Trastuzumab

Reporting group description:

Non-anthracycline based regimen (Group 1A TCHH): participants received 6 cycles of docetaxel 75 milligrams per square meter (mg/m^2) intravenously (IV) along with carboplatin 6 milligrams per milliliter per minute (mg/mL/min) area under the curve (AUC) IV, every three weeks (q3w) plus (+) trastuzumab (first dose: 8 milligrams per kilogram [mg/kg] IV and then 6 mg/kg IV) followed by trastuzumab alone (6 mg/kg) every 3 weeks to complete one year of therapy.
Anthracycline based regimen (Group 2A: THFECH): participants received 3 cycles q3w of trastuzumab (first dose: 8 mg/kg Cycle 1 and 6 mg/kg Doses 2 and 3) and docetaxel 100 mg/m^2 IV followed by 3 cycles q3w of 5-Fluorouracil (5-FU) 600 mg/m^2 IV push; epirubicin 90 mg/m^2 IV; cyclophosphamide 600 mg/m^2 IV and then trastuzumab alone (Dose 4: 8 mg/kg Cycle 1 and then 6 mg/kg) q3w to complete one year of therapy.

Reporting group title	Chemotherapy + Trastuzumab + Bevacizumab

Reporting group description:

Non-anthracycline based regimen (Group 1B:TCHBHB): Participants received 6 cycles of docetaxel 75 mg/m^2 IV along with carboplatin 6 mg/mL/min AUC IV, q3w + trastuzumab (8 mg/kg IV in Cycle 1 and then 6 mg/kg IV) and bevacizumab (15 mg/kg IV) followed by trastuzumab (6 mg/kg) +bevacizumab (15 mg/kg IV) every 3 weeks to complete one year of therapy.
Anthracycline based regimen (Group 2B: THBFECHB): Participants received 3 cycles of q3w of trastuzumab (first dose: 8 mg/kg Cycle 1 and 6 mg/kg Doses 2 and 3), bevacizumab 15 mg/kg IV, and docetaxel 100 mg/m^2 IV followed by 3 cycles q3w of 5-FU 600 mg/m^2 IV push; epirubicin 90 mg/m^2 IV; cyclophosphamide 600 mg/m^2 IV and then trastuzumab (Dose 4: 8 mg/kg Cycle 1 and 6 mg/kg) and bevacizumab (15 mg/kg IV) every 3 weeks to complete one year of therapy.

Primary: Invasive Disease-Free Survival (IDFS) Time

End point title	Invasive Disease-Free Survival (IDFS) Time

End point description:

IDFS was defined as the time from randomization to local recurrence following mastectomy, invasive local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, invasive contralateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer. '9999' for median, '999' and '99999' for lower and upper range of 95% confidence interval (CI), respectively in results field signifies 'Not Available'; the median and 95% CI were not reached as majority of participants were censored. Intent-to-treat population (ITT) was defined as all participants who were randomized to study treatment irrespective of exposure to the assigned study treatment.

End point type	Primary

End point timeframe:

Every 12 months during targeted therapy and from completion of targeted therapy through Year 10 (until data cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Months				
median (confidence interval 95%)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

Statistical analysis title	IDFS Time
Comparison groups	Chemotherapy + Trastuzumab + Bevacizumab v Chemotherapy + Trastuzumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.961
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.25

Primary: Percentage of Participants With IDFS Events

End point title	Percentage of Participants With IDFS Events[1]

End point description:

IDFS was defined as the time from randomization to local recurrence following mastectomy, invasive local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, invasive contralateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer. ITT population was defined as all participants who were randomized to study treatment irrespective of exposure to the assigned study treatment.

End point type	Primary

End point timeframe:

Every 12 months during targeted therapy and from completion of targeted therapy through Year 10 (until data cutoff: 17 April 2014)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for the percentage of participants with an event.

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Percentage of participants				
number (not applicable)				
Percentage of Participants with Events	8.3	8.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS) Time

End point title	Disease-Free Survival (DFS) Time

End point description:

DFS was defined as the time from randomization to local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy (invasive or non-invasive), regional recurrence, distant recurrence, contralateral breast cancer (invasive or non-invasive), second primary cancer (other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer. ITT population was defined as all participants who were randomized to study treatment irrespective of exposure to the assigned study treatment. '9999' for median, '999' and '99999' for lower and upper range of 95% CI, respectively in results field signifies 'Not Available'; the median and 95% CI were not reached as majority of participants were censored.

End point type	Secondary

End point timeframe:

Every 12 months during targeted therapy and from completion of targeted therapy through Year 10 (until data cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Months				
median (confidence interval 95%)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

Statistical analysis title	DFS Time
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8402
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.29

Secondary: Percentage of Participants With DFS Event

End point title	Percentage of Participants With DFS Event

End point description:

DFS was defined as the time from randomization to local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy (invasive or non-invasive), regional recurrence, distant recurrence, contralateral breast cancer (invasive or non-invasive), second primary cancer (other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer. ITT population was defined as all participants who were randomized to study treatment irrespective of exposure to the assigned study treatment.

End point type	Secondary

End point timeframe:

Every 12 months during targeted therapy and from completion of targeted therapy through Year 10 (until data cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Percentage of participants				
number (not applicable)	8.3	8.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Time

End point title	Overall Survival (OS) Time

End point description:

OS was defined as the time from randomization to death from any cause. Participants without an event at the time of the clinical cutoff were censored at the last date the participant was known to be alive. ITT population was defined as all participants who were randomized to study treatment irrespective of exposure to the assigned study treatment. '9999' for median, '999' and '99999' for lower and upper range of 95% CI, respectively in results field signifies 'Not Available'; because the median and 95% CI was not reached as majority of participants were censored.

End point type	Secondary

End point timeframe:

Cycles 1-17, then every 6 months until Year 6 and every 12 months through year 10 (until cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Months				
median (confidence interval 95%)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

Statistical analysis title	OS Time
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5147
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.28

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

OS was defined as the time from randomization to death from any cause. Participants without an event at the time of the clinical cutoff were censored at the last date the participant was known to be alive. ITT population was defined as all participants who were randomized to study treatment irrespective of exposure to the assigned study treatment.

End point type	Secondary

End point timeframe:

Cycles 1-17, then every 6 months until Year 6 and every 12 months through year 10 (until cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Percentage of participants				
number (not applicable)	3.5	3.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence-Free Interval (RFI) Time

End point title	Recurrence-Free Interval (RFI) Time

End point description:

RFI was defined as the time from randomization until local, regional, or distant recurrence. Participants without an event at the time of the clinical cutoff were censored at the last date the participant was known to be event free. ITT population was defined as all participants who were randomized to study treatment irrespective of exposure to the assigned study treatment. '99999' for median, '999' and '99999' for lower and upper range of 95% CI, respectively in results field signifies 'Not Available'; because the median and 95% CI was not reached as majority of participants were censored.

End point type	Secondary

End point timeframe:

Every 12 months during targeted therapy and from completion of targeted therapy through Year 10 (until data cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Months				
median (confidence interval 95%)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

Statistical analysis title	RFI Time
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4331
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

Secondary: Percentage of Participants With Local, Regional, or Distant Recurrence

End point title	Percentage of Participants With Local, Regional, or Distant Recurrence

End point description:

RFI was defined as the time from randomization until local, regional, or distant recurrence. Participants without an event at the time of the clinical cutoff were censored at the last date the participant was known to be event free. ITT population was defined as all participants who were randomized to study treatment irrespective of exposure to the assigned study treatment.

End point type	Secondary

End point timeframe:

Every 12 months during targeted therapy and from completion of targeted therapy through Year 10 (until data cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Percentage of participants				
number (not applicable)	6.3	7.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Recurrence-Free Interval (DRFI) Time

End point title	Distant Recurrence-Free Interval (DRFI) Time

End point description:

DRFI was defined as the time from randomization until distant disease recurrence only. Participants without an event at the time of the clinical cutoff were censored at the last date the participant was known to be event free. ITT population was defined as all participants who were randomized to study treatment irrespective of exposure to the assigned study treatment. '9999' for median, '999' and '99999' for lower and upper range of 95% CI, respectively in results field signifies 'Not Available'; because the median and 95% CI was not reached as majority of participants were censored.

End point type	Secondary

End point timeframe:

Every 12 months during targeted therapy and from completion of targeted therapy through Year 10 (until data cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Months				
median (confidence interval 95%)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

Statistical analysis title	DRFI Time
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5829
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.43

Secondary: Percentage of Participants With Distant Recurrence

End point title	Percentage of Participants With Distant Recurrence

End point description:

DRFI was defined as the time from randomization until distant disease recurrence only. Participants without an event at the time of the clinical cutoff were censored at the last date the participant was known to be event free. ITT population was defined as all participants who were randomized to study treatment irrespective of exposure to the assigned study treatment.

End point type	Secondary

End point timeframe:

Every 12 months during targeted therapy and from completion of targeted therapy through Year 10 (until data cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Percentage of participants				
number (not applicable)				
Percentage of Participants with Events	5.4	5.9		

Percentage of Participants without Events	94.6	94.1		

Statistical analyses

No statistical analyses for this end point

Secondary: IDFS by Treatment and Biomarker Levels

End point title	IDFS by Treatment and Biomarker Levels

End point description:

IDFS was defined as the time from randomization to local recurrence following mastectomy, invasive local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, invasive contralateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer. The baseline sample median biomarker concentration was used as the cut point to group participants as high (greater than median) versus low (less than or equal to median) levels of concentration. The Biomarker Evaluable Protein Plasma Population (BEP) was defined as all participants in the ITT population who received any component of study medication and had a baseline biomarker sample available for analysis. '9999' for median, '999' and '99999' for lower and upper range of

End point type	Secondary

End point timeframe:

Every 12 months during targeted therapy and from completion of targeted therapy through Year 10 (until data cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1757	1752		
Units: Months				
median (confidence interval 95%)				
E-selectin (High level)	9999 (999 to 99999)	9999 (999 to 99999)		
E-selectin (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		
Intercellular cell adhesion molecule 1(High level)	9999 (999 to 99999)	9999 (999 to 99999)		
Intercellular cell adhesion molecule 1 (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		
Interleukin-8 (High level)	9999 (999 to 99999)	9999 (999 to 99999)		
Interleukin-8 (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		
Platelet-derived growth factor-C (High level)	9999 (999 to 99999)	9999 (999 to 99999)		
Platelet-derived growth factor-C (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		
Placental growth factor (High level)	9999 (999 to 99999)	9999 (999 to 99999)		
Placental growth factor (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		

Vascular endothelial growth factor-A (High level)	9999 (999 to 99999)	9999 (999 to 99999)		
Vascular endothelial growth factor-A (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		
Vascular endothelial growth factor-C (High level)	9999 (999 to 99999)	9999 (999 to 99999)		
Vascular endothelial growth factor-C (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		
VEFGR-1 (High level)	9999 (999 to 99999)	9999 (999 to 99999)		
VEFGR-1 (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		
VEFGR-2 (High level)	9999 (999 to 99999)	9999 (999 to 99999)		
VEFGR-2 (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		
VEFGR-3 (High level)	9999 (999 to 99999)	9999 (999 to 99999)		
VEFGR-3 (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		
Basic fibroblast growth factor (High level)	9999 (999 to 99999)	9999 (999 to 99999)		
Basic fibroblast growth factor (Low level)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

Statistical analysis title	E-selectin (High level)
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0328
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	6.22

Statistical analysis title	E-selectin (Low level)
Statistical analysis description:	
Number of participants for this analysis were 149 and 155 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab

Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9234
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	2.61

Statistical analysis title	Intercellular cell adhesion molecule 1(High level)
Statistical analysis description:	
Number of participants for this analysis were 156 and 147 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2161
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	3.74

Statistical analysis title	Intercellular cell adhesion molecule 1(Low level)
Statistical analysis description:	
Number of participants for this analysis were 149 and 155 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2397
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	4.95

Statistical analysis title	Interleukin-8 (High level)
Statistical analysis description:	
Number of participants for this analysis were 235 and 230 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7089
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.76

Statistical analysis title	Interleukin-8 (Low level)
Statistical analysis description:	
Number of participants for this analysis were 235 and 232 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3652
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	2.7

Statistical analysis title	Platelet-derived growth factor-C (High level)

Statistical analysis description:

Number of participants for this analysis were 234 and 235 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.

Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8598
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	2.26

Statistical analysis title	Platelet-derived growth factor-C (Low level)

Statistical analysis description:

Number of participants for this analysis were 239 and 230 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.

Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.593
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	2.23

Statistical analysis title	Placental growth factor (High level)

Statistical analysis description:

Number of participants for this analysis were 126 and 119 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.

Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab

Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0994
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	6.77

Statistical analysis title	Placental growth factor (Low level)
Statistical analysis description:	
Number of participants for this analysis were 179 and 183 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5226
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.82

Statistical analysis title	Vascular endothelial growth factor-A (High level)
Statistical analysis description:	
Number of participants for this analysis were 242 and 220 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8603
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	2.02

Statistical analysis title	Vascular endothelial growth factor-A (Low level)
Statistical analysis description:	
Number of participants for this analysis were 226 and 237 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.548
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	2.78

Statistical analysis title	Vascular endothelial growth factor-C (High level)
Statistical analysis description:	
Number of participants for this analysis were 229 and 240 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7868
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	2.16

Statistical analysis title	Vascular endothelial growth factor-C (Low level)

Statistical analysis description:

Number of participants for this analysis were 244 and 225 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.

Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6216
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.43

Statistical analysis title	VEFGR-1 (High level)

Statistical analysis description:

Number of participants for this analysis were 210 and 211 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.

Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.446
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	2.63

Statistical analysis title	VEFGR-1 (Low level)

Statistical analysis description:

Number of participants for this analysis were 260 and 251 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.

Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab

Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7039
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.75

Statistical analysis title	VEFGR-2 (High level)
Statistical analysis description:	
Number of participants for this analysis were 245 and 221 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1997
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.28

Statistical analysis title	VEFGR-2 (Low level)
Statistical analysis description:	
Number of participants for this analysis were 225 and 241 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0383
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	4.65

Statistical analysis title	VEFGR-3 (High level)
Statistical analysis description:	
Number of participants for this analysis were 238 and 228 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5419
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	2.5

Statistical analysis title	VEFGR-3 (Low level)
Statistical analysis description:	
Number of participants for this analysis were 232 and 234 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.	
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8534
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	2.11

Statistical analysis title	Basic fibroblast growth factor (High level)

Statistical analysis description:

Number of participants for this analysis were 235 and 231 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.

Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2761
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.36

Statistical analysis title	Basic fibroblast growth factor (Low level)

Statistical analysis description:

Number of participants for this analysis were 235 and 231 for Chemotherapy + Trastuzumab and Chemotherapy + Trastuzumab + Bevacizumab, respectively instead of 3509.

Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	4.46

Secondary: Percentage of Participants with Cardiac Events

End point title	Percentage of Participants with Cardiac Events

End point description:

The number of participants with cardiac toxicity was defined as those who had cardiac events of North Hampton Youth Association (NHYA) III and IV of left ventricular dysfunction (LVD) and/or who had definite or probable cardiac death. Other cardiac events included Grade 3 or 4 cardiac ischemia/infarction and Grade 3 systolic or diastolic dysfunction with NYHA Class II symptoms. The safety population consisted of all participants who received any study treatment, which was defined as at least one full or partial dose of bevacizumab, trastuzumab, docetaxel, carboplatin, or FEC.

End point type	Secondary

End point timeframe:

Within 3 days before each chemotherapy cycle from Cycle 2, 2-3 weeks after last chemotherapy dose during targeted therapy, every 6, 12 months from completion of targeted therapy through Year 5 and Years 6, respectively (until data cutoff 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1750	1722		
Units: Percentage of participants				
number (confidence interval 95%)				
Percentage of Participants with Events	25.5 (23 to 28)	51.3 (49 to 54)		

Statistical analyses

Statistical analysis title	Percentage of Participants With Cardiac Events
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3472
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Fisher exact

Secondary: IDFS Within Chemotherapy Cohorts

End point title	IDFS Within Chemotherapy Cohorts

End point description:

IDFS was defined as the time from randomization to local recurrence following mastectomy, invasive local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, invasive contralateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause prior to recurrence or second primary cancer. IDFS was identified within chemotherapy cohort of docetaxel/carboplatin plus trastuzumab with or without bevacizumab and of docetaxel plus trastuzumab given with or without bevacizumab followed by 5-FU, epirubicin, cyclophosphamide (FEC). ITT population was defined as all participants who were randomized to study treatment irrespective of exposure to the
assigned study treatment.

End point type	Secondary

End point timeframe:

Every 12 months during targeted therapy and from completion of targeted therapy through Year 10 (until data cutoff: 17 April 2014)

End point values	Chemotherapy + Trastuzumab	Chemotherapy + Trastuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1606[2]	1605[3]		
Units: Months				
median (confidence interval 95%)				
Docetaxel+Carboplatin+Trastuzumab; n=1606,1605	9999 (999 to 99999)	9999 (999 to 99999)		
Docetaxel+Trastuzumab+FEC; n=134,127	9999 (999 to 99999)	9999 (999 to 99999)		

Notes:

[2] - n (number) = participants analyzed at specified time for this endpoint.

[3] - n (number) = participants analyzed at specified time for this endpoint.

Statistical analyses

Statistical analysis title	Non-Antracycline based regimen
Comparison groups	Chemotherapy + Trastuzumab v Chemotherapy + Trastuzumab + Bevacizumab
Number of subjects included in analysis	3211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9354
Method	Logrank (stratified)
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.28

Statistical analysis title	Antracycline based regimen
Comparison groups	Chemotherapy + Trastuzumab + Bevacizumab v Chemotherapy + Trastuzumab
Number of subjects included in analysis	3211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5164
Method	Logrank (stratified)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.73

Adverse events information

Timeframe for reporting adverse events:

From baseline to the end of study (74 months)

Adverse event reporting additional description:

The Safety Population consisted of all participants who received any study treatment, which was defined as at least one full or partial dose of bevacizumab, trastuzumab, docetaxel, carboplatin, or FEC.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Safety Cohort 1: Chemo + Trastuzumab (<18 month)

Reporting group description:

Safety Cohort 1 was set up with first 300 enrolled from Group 1 (non anthracycline regimen) and the first 278 participants from Group 2 (anthracycline regimen). This reporting group included participants in Safety Cohort 1 who received chemo+trastuzumab (H) but no bevacizumab (B). Participants from Group 1 (TCHH) received: 6 q3w cycles of docetaxel (T; 75 mg/m^2) IV+carboplatin (C;6 mg/mL/min) AUC IV, with q3w 1-year of H (8 mg/kg in Cycle 1 and then 6 mg/kg) IV. Participants from Group 2 (THFECH) received: 3 q3w cycles of H (8 mg/kg dose 1, 6 mg/kg doses 2 & 3) IV + T (100 mg/m^2 IV), then 3 q3w cycles of 5-FU (600 mg/m^2) IV + epirubicin (90 mg/m^2) IV + cyclophosphamide (600 mg/m^2) IV, and then H alone q3w (8 mg/kg dose 4, then 6 mg/kg) IV to complete 1 year of therapy. In this safety cohort, all grades of AEs until 18 months after randomization were collected and reported.

Reporting group title	Safety Cohort 1: Chemo + Trastuzumab + Bevacizumab (<18 month)

Reporting group description:

Safety Cohort 1 was set up with the first 300 participants enrolled from Group 1 (non anthracycline regimen) and the first 278 participants from Group 2 (anthracycline regimen). This reporting group included participants in Safety Cohort 1 who received B with chemo+H. Participants from Group 1 (TCHBHB) received: 6 q3w cycles of T (75 mg/m^2) IV + C (6 mg/mL/min) AUC IV, with q3w 1-year of H (8 mg/kg in Cycle 1 and then 6 mg/kg) IV + B (15 mg/kg) IV. Participants from Group 2 (THBFECH) received: 3 q3w cycles of H (8 mg/kg dose 1, 6 mg/kg doses 2 & 3) IV + T (100 mg/m^2 IV) + B (15 mg/kg), then 3 q3w cycles of 5-FU (600 mg/m^2) IV + epirubicin (90 mg/m^2) IV + cyclophosphamide (600 mg/m^2) IV, and then q3w B (15 mg/kg) + H (8 mg/kg dose 4, then 6 mg/kg) IV to complete 1 year of therapy. In this safety cohort, all grades of AEs until 18 months after randomization were collected and are reported in this

Reporting group title	Safety Cohort 2: Chemo + Trastuzumab (<18 months)

Reporting group description:

Safety Cohort 2 was set up with participants enrolled after the first 300 participants in each group of chemotherapy which correspond to 2931 participants from Group 1 (non anthracycline regimen [TCHH or TCHBHB]). This reporting group included participants in Safety Cohort 2 who received chemo+H but no B, i.e. TCHH. Participants from Group 1 (TCHH) received: 6 q3w cycles of T (75 mg/m^2) IV + C (6 mg/mL/min) AUC IV, with q3w 1-year of H (8 mg/kg in Cycle 1 and then 6 mg/kg) IV. In this safety cohort, until 18 months after randomization, only the following adverse events (AEs) were collected: Grade >=2 AE Special Interest (AESI); Grade 1 and 2 AEs requiring change in treatment (i.e. delay in treatment, a dose reduction, or discontinuation of one or more of the study therapy drugs); and all Grade 3 and 4 AE. And they are reported in this reporting group.

Reporting group title	Safety Cohort 2: Chemo + Trastuzumab + Bevacizumab(<18 months)

Reporting group description:

Safety Cohort 2 was set up with participants enrolled after the first 300 participants in each group of chemotherapy which correspond to 2931 participants from Group 1 (non anthracycline regimen [TCHH or TCHBHB]). This reporting group included participants who received B with chemo+H, i.e. TCHBHB. Participants from Group 1 (TCHBHB) received: 6 q3w cycles of T (75 mg/m^2) IV + C (6 mg/mL/min) AUC IV, with q3w 1-year of H (8 mg/kg in Cycle 1 and then 6 mg/kg) IV + B (15 mg/kg) IV. In this safety cohort, until 18 months after randomization, only the following AEs were collected: Grade >=2 AESI; Grade 1 and 2 AEs requiring change in treatment (i.e. delay in treatment, a dose reduction, or discontinuation of one or more of the study therapy drugs); and all Grade 3 and 4 AE. And

they are reported in this reporting group.

Reporting group title	Chemotherapy + Trastuzumab (>18 months)

Reporting group description:

After 18 months of observation period, the AE collection requirement was the same in both Safety Cohort 1 and 2: Grade >=2 AESI and treatment related Grade 3 and 4 AEs. All collected AEs after 18 months are reported in this reporting group. This reporting group included participants in both Safety Cohort 1 and 2 who received chemo+H but no B, i.e. TCHH and THFECH. Participants from Group 1 (TCHH) received 6 q3w cycles of T (75 mg/m^2) IV + C (6 mg/mL/min) AUC IV, with q3w 1-year of H (8 mg/kg in Cycle 1 and then 6 mg/kg) IV. Participants from Group 2 (THFECH) received 3 q3w cycles of H (8 mg/kg dose 1, 6 mg/kg doses 2 & 3) IV + T (100 mg/m^2 IV), then 3 q3w cycles of 5-FU (600 mg/m^2) IV + epirubicin (90 mg/m^2) IV + cyclophosphamide (600 mg/m^2) IV, and then H alone q3w (8 mg/kg dose 4, then 6 mg/kg) IV to complete 1 year of therapy.

Reporting group title	Chemotherapy + Trastuzumab + Bevacizumab (>18 months)

Reporting group description:

After 18 months observation period, the AE collection requirement was same in both Safety Cohort 1 and 2: Grade >=2 AESI and treatment related Grade 3 and 4 AEs. All collected AEs after 18 months are reported in this reporting group which included participants in Safety Cohort 1 and 2 who received B with chemo+H (TCHBHB and THBFECHB). Participants from Group 1 (TCHBHB) received 6 q3w cycles of T (75 mg/m^2) IV + C (6 mg/mL/min) AUC IV, with q3w 1-year of H (8 mg/kg in Cycle 1 and then 6 mg/kg) IV + B (15 mg/kg) IV. Participants from Group 2 (THBFECHB) received 3 q3w cycles of H (8 mg/kg dose 1, 6 mg/kg doses 2 & 3) IV + T (100 mg/m^2 IV) + B (15 mg/kg), then 3 q3w cycles of 5-FU (600 mg/m^2) IV + epirubicin (90 mg/m^2) IV + cyclophosphamide (600 mg/m^2) IV, and then q3w B (15 mg/kg) + H (8 mg/kg dose 4, then 6 mg/kg) IV to complete 1 year of therapy.

Serious adverse events	Safety Cohort 1: Chemo + Trastuzumab (<18 month)	Safety Cohort 1: Chemo + Trastuzumab + Bevacizumab (<18 month)	Safety Cohort 2: Chemo + Trastuzumab (<18 months)
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 289 (22.15%)	98 / 286 (34.27%)	345 / 1461 (23.61%)
number of deaths (all causes)	10	15	49
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neurilemmoma benign			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Carcinoid tumour			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Fibroadenoma of breast			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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

Haemangioma of liver			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 289 (0.35%)	1 / 286 (0.35%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 289 (0.35%)	1 / 286 (0.35%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	4 / 1461 (0.27%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Jugular vein thrombosis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoedema			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Axillary vein thrombosis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Haemorrhage			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Thrombophlebitis superficial			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Surgical and medical procedures			
Endotracheal intubation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 289 (0.00%)	3 / 286 (1.05%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 289 (0.35%)	1 / 286 (0.35%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 289 (0.69%)	0 / 286 (0.00%)	7 / 1461 (0.48%)
occurrences causally related to treatment / all	1 / 2	0 / 0	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device breakage			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
General physical health deterioration			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General symptom			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Impaired healing			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Medical device complication			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Mucosal inflammation			

subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Sudden death			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Thrombosis in device			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Asthenia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Influenza like illness			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
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 complication associated with device			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Chills			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Discomfort			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Extravasation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Facial pain			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Ulcer haemorrhage			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	1 / 289 (0.35%)	2 / 286 (0.70%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 289 (0.00%)	2 / 286 (0.70%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	6 / 6	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Menorrhagia			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Breast calcifications			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mammary fistula			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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 cyst			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 289 (0.35%)	2 / 286 (0.70%)	0 / 1461 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 289 (0.35%)	2 / 286 (0.70%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	1 / 1	1 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 289 (0.00%)	2 / 286 (0.70%)	0 / 1461 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Hypoxia			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Laryngeal oedema			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Nasal septum perforation			

subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Pleural effusion			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Pulmonary congestion			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Respiratory arrest			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Interstitial lung disease			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Bronchospasm			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial hyperreactivity			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Dysphonia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Hyperventilation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Pleurisy			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
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 failure			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 289 (0.35%)	2 / 286 (0.70%)	4 / 1461 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Hallucination			

subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Confusional state			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute psychosis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood altered			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Psychiatric decompensation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Suicide attempt			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Blood creatinine increased			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Carbon monoxide diffusing capacity decreased			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Liver function test abnormal			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Weight decreased			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	1 / 289 (0.35%)	1 / 286 (0.35%)	0 / 1461 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Fall			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Femoral neck fracture			

subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Foot fracture			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Road traffic accident			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Spinal compression fracture			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Wound dehiscence			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Wound complication			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia postoperative			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Ankle fracture			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
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 haematoma			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Incisional hernia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Overdose			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Cerebrovascular arteriovenous malformation			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuropericarditis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Palpitations			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac valve disease			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Cardiopulmonary failure			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracardiac thrombus			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Restrictive cardiomyopathy			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular dysfunction			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Tachycardia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Torsade de pointes			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Ventricular arrhythmia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Supraventricular tachyarrhythmia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 289 (0.00%)	2 / 286 (0.70%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intercostal neuralgia			

subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Syncope			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	5 / 1461 (0.34%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Presyncope			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Aphasia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Cerebral infarction			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Intracranial pressure increased			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Ischaemic stroke			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Paraesthesia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Sensorimotor disorder			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	18 / 289 (6.23%)	22 / 286 (7.69%)	74 / 1461 (5.07%)
occurrences causally related to treatment / all	18 / 18	28 / 28	79 / 79
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	9 / 289 (3.11%)	16 / 286 (5.59%)	54 / 1461 (3.70%)
occurrences causally related to treatment / all	9 / 9	17 / 17	55 / 55
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			

subjects affected / exposed	5 / 289 (1.73%)	0 / 286 (0.00%)	9 / 1461 (0.62%)
occurrences causally related to treatment / all	5 / 5	0 / 0	10 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 289 (0.35%)	2 / 286 (0.70%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	1 / 1	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	7 / 1461 (0.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulocytopenia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Lymphadenopathy			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 289 (0.35%)	1 / 286 (0.35%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Corneal perforation			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Dacryostenosis acquired			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid function disorder			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Intraocular haematoma			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Oscillopsia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Retinal detachment			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
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			
Diarrhoea			
subjects affected / exposed	9 / 289 (3.11%)	7 / 286 (2.45%)	24 / 1461 (1.64%)
occurrences causally related to treatment / all	10 / 10	7 / 8	26 / 30
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	4 / 289 (1.38%)	3 / 286 (1.05%)	14 / 1461 (0.96%)
occurrences causally related to treatment / all	5 / 5	4 / 4	14 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 289 (1.04%)	2 / 286 (0.70%)	6 / 1461 (0.41%)
occurrences causally related to treatment / all	3 / 3	3 / 3	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 289 (0.00%)	3 / 286 (1.05%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 289 (0.00%)	2 / 286 (0.70%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 289 (0.00%)	2 / 286 (0.70%)	0 / 1461 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Gastroduodenal ulcer			

subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Ileus			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal ulcer			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Large intestine perforation			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Pancreatitis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Stomatitis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastritis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Abdominal distension			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Colitis ulcerative			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Dyspepsia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Dysphagia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Gastrointestinal toxicity			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Intestinal ischaemia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Intestinal perforation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Neutropenic colitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Subileus			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Cholecystitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Cholecystitis acute			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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 function abnormal			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Hepatobiliary disease			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Skin and subcutaneous tissue disorders			

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Rash maculo-papular			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Rash			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Cold sweat			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Nail disorder			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain of skin			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Rash generalised			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Rash pruritic			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Rash vesicular			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin atrophy			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Skin disorder			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Skin exfoliation			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Skin ulcer			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Urticaria			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
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 and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 289 (0.35%)	1 / 286 (0.35%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			

subjects affected / exposed	2 / 289 (0.69%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	1 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Haematuria			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerulosclerosis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Prerenal failure			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
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 colic			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Urinary retention			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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 pain			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Arthralgia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Flank pain			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Musculoskeletal chest pain			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Musculoskeletal stiffness			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Myositis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scleroderma			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Neutropenic infection			
subjects affected / exposed	0 / 289 (0.00%)	8 / 286 (2.80%)	33 / 1461 (2.26%)
occurrences causally related to treatment / all	0 / 0	8 / 8	31 / 34
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Urinary tract infection			

subjects affected / exposed	1 / 289 (0.35%)	6 / 286 (2.10%)	11 / 1461 (0.75%)
occurrences causally related to treatment / all	1 / 1	2 / 6	2 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 289 (0.69%)	1 / 286 (0.35%)	5 / 1461 (0.34%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 289 (0.35%)	2 / 286 (0.70%)	6 / 1461 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 289 (0.00%)	2 / 286 (0.70%)	0 / 1461 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 289 (0.35%)	1 / 286 (0.35%)	4 / 1461 (0.27%)
occurrences causally related to treatment / all	0 / 1	1 / 1	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 289 (0.35%)	1 / 286 (0.35%)	0 / 1461 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 289 (0.35%)	1 / 286 (0.35%)	5 / 1461 (0.34%)
occurrences causally related to treatment / all	3 / 3	0 / 1	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 289 (0.35%)	1 / 286 (0.35%)	4 / 1461 (0.27%)
occurrences causally related to treatment / all	1 / 1	0 / 1	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute tonsillitis			

subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Anal abscess			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Febrile infection			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	4 / 1461 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected cyst			

subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Influenza			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Localised infection			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Mastitis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Rectal abscess			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Respiratory tract infection			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			

subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	0 / 1461 (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
Tooth abscess			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	0 / 1461 (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
Viral infection			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	4 / 1461 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	3 / 3
Neutropenic sepsis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
H1N1 influenza			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blister infected			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Cellulitis staphylococcal			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Post procedural infection			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
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 infection			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Staphylococcal infection			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Staphylococcal sepsis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
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	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal sepsis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Acute sinusitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Arthritis infective			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blastocystis infection			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cellulitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Bronchitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Genital infection			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Herpes virus infection			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Herpes zoster			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Oesophageal candidiasis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Otitis media			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Paronychia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Periodontitis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Peritonsillitis			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Pharyngitis streptococcal			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia escherichia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Proctitis infectious			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Pyelonephritis			

subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Rickettsiosis			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Staphylococcal skin infection			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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			
subjects affected / exposed	2 / 289 (0.69%)	4 / 286 (1.40%)	9 / 1461 (0.62%)
occurrences causally related to treatment / all	3 / 3	3 / 4	7 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 289 (0.35%)	0 / 286 (0.00%)	3 / 1461 (0.21%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			

subjects affected / exposed	0 / 289 (0.00%)	1 / 286 (0.35%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	2 / 1461 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Failure to thrive			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	0 / 1461 (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
Hypomagnesaemia			
subjects affected / exposed	0 / 289 (0.00%)	0 / 286 (0.00%)	1 / 1461 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Safety Cohort 2: Chemo + Trastuzumab + Bevacizumab(<18 months)	Chemotherapy + Trastuzumab (>18 months)	Chemotherapy + Trastuzumab + Bevacizumab (>18 months)
Total subjects affected by serious adverse events			
subjects affected / exposed	474 / 1436 (33.01%)	1 / 1750 (0.06%)	3 / 1722 (0.17%)
number of deaths (all causes)	46	14	14
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neurilemmoma benign			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Carcinoid tumour			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Fibroadenoma of breast			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Haemangioma of liver			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Deep vein thrombosis			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Hypertension			

subjects affected / exposed	5 / 1436 (0.35%)	0 / 1750 (0.00%)	1 / 1722 (0.06%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Subclavian vein thrombosis			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Lymphoedema			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Axillary vein thrombosis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Embolism			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Haemorrhage			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Hypertensive crisis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Thrombophlebitis superficial			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Endotracheal intubation			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 1436 (0.49%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	8 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	13 / 1436 (0.91%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	8 / 13	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device breakage			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
General physical health deterioration			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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

General symptom			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Impaired healing			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Medical device complication			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Mucosal inflammation			
subjects affected / exposed	7 / 1436 (0.49%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	7 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Pain			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Sudden death			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Thrombosis in device			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Multi-organ failure			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Asthenia			
subjects affected / exposed	7 / 1436 (0.49%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	7 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Influenza like illness			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast complication associated with device			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Chills			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Discomfort			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Extravasation			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Facial pain			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Ulcer haemorrhage			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Hypersensitivity			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Anaphylactic reaction			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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			
Adnexa uteri mass			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Menorrhagia			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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

Uterine haemorrhage			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Breast calcifications			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Mammary fistula			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Ovarian cyst			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Haemoptysis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Epistaxis			
subjects affected / exposed	5 / 1436 (0.35%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypoxia			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Laryngeal oedema			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Lung disorder			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Nasal septum perforation			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Pulmonary congestion			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Respiratory arrest			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Interstitial lung disease			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Aspiration			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Bronchospasm			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Bronchial hyperreactivity			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Cough			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Dysphonia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Hyperventilation			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Pleurisy			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Respiratory failure			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Hallucination			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Confusional state			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Acute psychosis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Insomnia			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Mood altered			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Psychiatric decompensation			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Suicide attempt			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Blood creatinine increased			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Carbon monoxide diffusing capacity decreased			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Lipase			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Liver function test abnormal			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Weight decreased			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Injury, poisoning and procedural complications			

Seroma			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Accidental overdose			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Foot fracture			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Road traffic accident			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Spinal compression fracture			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Wound dehiscence			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Wound complication			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Humerus fracture			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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 limb fracture			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Anaemia postoperative			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Ankle fracture			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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 haematoma			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Incisional hernia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Overdose			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Patella fracture			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Radius fracture			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Congenital, familial and genetic disorders			
Cerebrovascular arteriovenous malformation			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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			
Left ventricular dysfunction			
subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	1 / 1722 (0.06%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuropericarditis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Supraventricular tachycardia			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac arrest			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Palpitations			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Atrial fibrillation			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Bradycardia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Pericarditis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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 valve disease			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	1 / 1722 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Cardiopulmonary failure			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Intracardiac thrombus			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Restrictive cardiomyopathy			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Right ventricular dysfunction			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Tachycardia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Torsade de pointes			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Ventricular arrhythmia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Supraventricular tachyarrhythmia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Acute myocardial infarction			

subjects affected / exposed	0 / 1436 (0.00%)	1 / 1750 (0.06%)	0 / 1722 (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
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Dizziness			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Intercostal neuralgia			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Syncope			
subjects affected / exposed	7 / 1436 (0.49%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	4 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Neuropathy peripheral			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			

subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Aphasia			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Cognitive disorder			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Convulsion			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Encephalopathy			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Intracranial pressure increased			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Ischaemic stroke			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Lethargy			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Migraine			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Paraesthesia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Sensorimotor disorder			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Tremor			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	120 / 1436 (8.36%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	124 / 124	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	84 / 1436 (5.85%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	90 / 90	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	7 / 1436 (0.49%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	6 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	12 / 1436 (0.84%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	12 / 12	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	6 / 1436 (0.42%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Febrile bone marrow aplasia			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Granulocytopenia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Lymphadenopathy			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Eye disorders			
Corneal perforation			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Dacryostenosis acquired			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Eyelid function disorder			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Intraocular haematoma			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Oscillopsia			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Retinal detachment			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	31 / 1436 (2.16%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	31 / 36	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	20 / 1436 (1.39%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	20 / 23	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	6 / 1436 (0.42%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	9 / 1436 (0.63%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	6 / 11	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Oesophagitis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Abdominal pain upper			

subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Gastric perforation			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Gastric ulcer			
subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroduodenal ulcer			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Ileus			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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 ulcer			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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 intestine perforation			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Pancreatitis			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Stomatitis			
subjects affected / exposed	5 / 1436 (0.35%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Gastritis			
subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Constipation			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Haematemesis			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Haemorrhoids			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Rectal haemorrhage			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Abdominal distension			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Colitis ulcerative			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Duodenal ulcer perforation			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Dyspepsia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Dysphagia			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Faecaloma			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Gastric haemorrhage			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Gastrointestinal toxicity			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Ileus paralytic			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Intestinal ischaemia			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Intestinal perforation			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Neutropenic colitis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Pancreatitis acute			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Subileus			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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 failure			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Cholecystitis			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Hepatic function abnormal			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Hepatobiliary disease			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Rash maculo-papular			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Rash			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cold sweat			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Erythema			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nail disorder			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Rash generalised			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Rash pruritic			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Rash vesicular			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Skin atrophy			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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 disorder			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Skin exfoliation			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Skin ulcer			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Urticaria			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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 failure acute			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Calculus ureteric			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Haematuria			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Glomerulosclerosis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Prerenal failure			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Renal colic			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Urinary retention			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Neck pain			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Spinal pain			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Arthralgia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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

Intervertebral disc protrusion			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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 pain			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Myalgia			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Osteoarthritis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Pain in extremity			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Flank pain			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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 chest pain			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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 stiffness			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Myositis			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Scleroderma			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Infections and infestations			
Neutropenic infection			
subjects affected / exposed	45 / 1436 (3.13%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	44 / 46	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	6 / 1436 (0.42%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	4 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	13 / 1436 (0.91%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	3 / 13	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Infection			
subjects affected / exposed	10 / 1436 (0.70%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	6 / 10	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Pneumonia			
subjects affected / exposed	8 / 1436 (0.56%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	3 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Acute tonsillitis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Anal abscess			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Device related sepsis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Diverticulitis			

subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Gastroenteritis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Infected cyst			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Influenza			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Kidney infection			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Localised infection			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Mastitis			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Rectal abscess			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Respiratory tract infection			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Salmonellosis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Tooth abscess			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Urosepsis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Viral infection			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Neutropenic sepsis			

subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
H1N1 influenza			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Wound infection			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Sinusitis			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Abscess			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Blister infected			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Cellulitis staphylococcal			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Clostridium difficile infection			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Postoperative wound infection			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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 infection			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Staphylococcal infection			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Staphylococcal sepsis			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Subcutaneous abscess			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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 respiratory tract infection			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Abdominal sepsis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Acute sinusitis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Appendicitis perforated			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Arthritis infective			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Atypical pneumonia			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Blastocystis infection			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Breast cellulitis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Bronchitis			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Cystitis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Endocarditis			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Genital infection			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Herpes virus infection			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Herpes zoster			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Oesophageal candidiasis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Otitis media			

subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Paronychia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Periodontitis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Peritonsillitis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Pharyngitis streptococcal			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Pneumonia escherichia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Proctitis infectious			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Pseudomonal bacteraemia			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Pseudomonas infection			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Pulmonary tuberculosis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Pyelonephritis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Pyelonephritis acute			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Rickettsiosis			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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 skin infection			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	10 / 1436 (0.70%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	17 / 17	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Hyponatraemia			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (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
Hypovolaemia			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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
Decreased appetite			
subjects affected / exposed	5 / 1436 (0.35%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences causally related to treatment / all	4 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Failure to thrive			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Hyperglycaemia			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (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
Hypomagnesaemia			

subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (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

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

Non-serious adverse events	Safety Cohort 1: Chemo + Trastuzumab (<18 month)	Safety Cohort 1: Chemo + Trastuzumab + Bevacizumab (<18 month)	Safety Cohort 2: Chemo + Trastuzumab (<18 months)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	278 / 289 (96.19%)	271 / 286 (94.76%)	950 / 1461 (65.02%)
Vascular disorders			
Hot flush			
subjects affected / exposed	68 / 289 (23.53%)	58 / 286 (20.28%)	16 / 1461 (1.10%)
occurrences (all)	71	60	16
Lymphoedema			
subjects affected / exposed	18 / 289 (6.23%)	16 / 286 (5.59%)	4 / 1461 (0.27%)
occurrences (all)	19	17	4
Flushing			
subjects affected / exposed	16 / 289 (5.54%)	11 / 286 (3.85%)	3 / 1461 (0.21%)
occurrences (all)	18	12	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	147 / 289 (50.87%)	162 / 286 (56.64%)	128 / 1461 (8.76%)
occurrences (all)	183	184	169
Mucosal inflammation			
subjects affected / exposed	69 / 289 (23.88%)	85 / 286 (29.72%)	30 / 1461 (2.05%)
occurrences (all)	99	112	33
Asthenia			
subjects affected / exposed	49 / 289 (16.96%)	38 / 286 (13.29%)	49 / 1461 (3.35%)
occurrences (all)	78	62	56
Pyrexia			
subjects affected / exposed	28 / 289 (9.69%)	47 / 286 (16.43%)	17 / 1461 (1.16%)
occurrences (all)	36	57	18
Oedema peripheral			

subjects affected / exposed	46 / 289 (15.92%)	27 / 286 (9.44%)	25 / 1461 (1.71%)
occurrences (all)	54	31	27
Oedema			
subjects affected / exposed	25 / 289 (8.65%)	15 / 286 (5.24%)	7 / 1461 (0.48%)
occurrences (all)	28	17	7
Pain			
subjects affected / exposed	20 / 289 (6.92%)	18 / 286 (6.29%)	8 / 1461 (0.55%)
occurrences (all)	23	19	8
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	17 / 289 (5.88%)	16 / 286 (5.59%)	34 / 1461 (2.33%)
occurrences (all)	22	21	41
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	22 / 289 (7.61%)	18 / 286 (6.29%)	100 / 1461 (6.84%)
occurrences (all)	23	18	102
Breast pain			
subjects affected / exposed	12 / 289 (4.15%)	15 / 286 (5.24%)	2 / 1461 (0.14%)
occurrences (all)	14	19	2
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	35 / 289 (12.11%)	116 / 286 (40.56%)	12 / 1461 (0.82%)
occurrences (all)	36	133	12
Cough			
subjects affected / exposed	56 / 289 (19.38%)	49 / 286 (17.13%)	3 / 1461 (0.21%)
occurrences (all)	59	53	3
Dyspnoea			
subjects affected / exposed	45 / 289 (15.57%)	40 / 286 (13.99%)	17 / 1461 (1.16%)
occurrences (all)	50	42	18
Oropharyngeal pain			
subjects affected / exposed	21 / 289 (7.27%)	36 / 286 (12.59%)	3 / 1461 (0.21%)
occurrences (all)	27	43	3
Respiratory tract haemorrhage			
subjects affected / exposed	3 / 289 (1.04%)	20 / 286 (6.99%)	0 / 1461 (0.00%)
occurrences (all)	3	24	0
Dysphonia			

subjects affected / exposed	5 / 289 (1.73%)	17 / 286 (5.94%)	1 / 1461 (0.07%)
occurrences (all)	5	18	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	61 / 289 (21.11%)	58 / 286 (20.28%)	13 / 1461 (0.89%)
occurrences (all)	64	64	13
Anxiety			
subjects affected / exposed	31 / 289 (10.73%)	22 / 286 (7.69%)	8 / 1461 (0.55%)
occurrences (all)	34	22	8
Depression			
subjects affected / exposed	23 / 289 (7.96%)	20 / 286 (6.99%)	6 / 1461 (0.41%)
occurrences (all)	24	21	6
Investigations			
Weight decreased			
subjects affected / exposed	15 / 289 (5.19%)	36 / 286 (12.59%)	2 / 1461 (0.14%)
occurrences (all)	15	37	2
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 289 (5.19%)	17 / 286 (5.94%)	28 / 1461 (1.92%)
occurrences (all)	18	22	32
Alanine aminotransferase increased			
subjects affected / exposed	16 / 289 (5.54%)	10 / 286 (3.50%)	22 / 1461 (1.51%)
occurrences (all)	18	12	25
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	39 / 289 (13.49%)	34 / 286 (11.89%)	8 / 1461 (0.55%)
occurrences (all)	39	36	8
Nervous system disorders			
Headache			
subjects affected / exposed	63 / 289 (21.80%)	90 / 286 (31.47%)	25 / 1461 (1.71%)
occurrences (all)	76	108	27
Dysgeusia			
subjects affected / exposed	60 / 289 (20.76%)	72 / 286 (25.17%)	14 / 1461 (0.96%)
occurrences (all)	72	78	15
Peripheral sensory neuropathy			
subjects affected / exposed	59 / 289 (20.42%)	61 / 286 (21.33%)	56 / 1461 (3.83%)
occurrences (all)	68	72	61

Dizziness			
subjects affected / exposed	46 / 289 (15.92%)	37 / 286 (12.94%)	15 / 1461 (1.03%)
occurrences (all)	58	48	15
Neuropathy peripheral			
subjects affected / exposed	32 / 289 (11.07%)	31 / 286 (10.84%)	33 / 1461 (2.26%)
occurrences (all)	37	34	39
Paraesthesia			
subjects affected / exposed	10 / 289 (3.46%)	21 / 286 (7.34%)	10 / 1461 (0.68%)
occurrences (all)	10	23	11
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	103 / 289 (35.64%)	84 / 286 (29.37%)	343 / 1461 (23.48%)
occurrences (all)	165	113	672
Anaemia			
subjects affected / exposed	89 / 289 (30.80%)	80 / 286 (27.97%)	198 / 1461 (13.55%)
occurrences (all)	108	86	218
Leukopenia			
subjects affected / exposed	63 / 289 (21.80%)	46 / 286 (16.08%)	122 / 1461 (8.35%)
occurrences (all)	106	58	215
Thrombocytopenia			
subjects affected / exposed	33 / 289 (11.42%)	41 / 286 (14.34%)	164 / 1461 (11.23%)
occurrences (all)	52	51	227
Eye disorders			
Lacrimation increased			
subjects affected / exposed	30 / 289 (10.38%)	52 / 286 (18.18%)	4 / 1461 (0.27%)
occurrences (all)	33	55	7
Vision blurred			
subjects affected / exposed	17 / 289 (5.88%)	10 / 286 (3.50%)	5 / 1461 (0.34%)
occurrences (all)	17	13	5
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	179 / 289 (61.94%)	170 / 286 (59.44%)	104 / 1461 (7.12%)
occurrences (all)	274	248	129
Diarrhoea			
subjects affected / exposed	136 / 289 (47.06%)	163 / 286 (56.99%)	148 / 1461 (10.13%)
occurrences (all)	180	221	177

Vomiting			
subjects affected / exposed	90 / 289 (31.14%)	93 / 286 (32.52%)	61 / 1461 (4.18%)
occurrences (all)	118	119	68
Constipation			
subjects affected / exposed	87 / 289 (30.10%)	84 / 286 (29.37%)	25 / 1461 (1.71%)
occurrences (all)	101	96	26
Stomatitis			
subjects affected / exposed	52 / 289 (17.99%)	77 / 286 (26.92%)	37 / 1461 (2.53%)
occurrences (all)	65	90	44
Dyspepsia			
subjects affected / exposed	46 / 289 (15.92%)	53 / 286 (18.53%)	20 / 1461 (1.37%)
occurrences (all)	54	58	21
Abdominal pain			
subjects affected / exposed	32 / 289 (11.07%)	36 / 286 (12.59%)	24 / 1461 (1.64%)
occurrences (all)	43	50	28
Abdominal pain upper			
subjects affected / exposed	21 / 289 (7.27%)	26 / 286 (9.09%)	12 / 1461 (0.82%)
occurrences (all)	26	29	14
Haemorrhoids			
subjects affected / exposed	8 / 289 (2.77%)	20 / 286 (6.99%)	4 / 1461 (0.27%)
occurrences (all)	9	21	4
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	182 / 289 (62.98%)	175 / 286 (61.19%)	95 / 1461 (6.50%)
occurrences (all)	190	181	97
Nail disorder			
subjects affected / exposed	60 / 289 (20.76%)	83 / 286 (29.02%)	4 / 1461 (0.27%)
occurrences (all)	61	86	5
Rash			
subjects affected / exposed	73 / 289 (25.26%)	59 / 286 (20.63%)	28 / 1461 (1.92%)
occurrences (all)	85	66	28
Dry skin			
subjects affected / exposed	20 / 289 (6.92%)	31 / 286 (10.84%)	2 / 1461 (0.14%)
occurrences (all)	21	33	2
Pruritus			

subjects affected / exposed	31 / 289 (10.73%)	18 / 286 (6.29%)	3 / 1461 (0.21%)
occurrences (all)	36	20	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	17 / 289 (5.88%)	23 / 286 (8.04%)	6 / 1461 (0.41%)
occurrences (all)	23	24	7
Erythema			
subjects affected / exposed	15 / 289 (5.19%)	15 / 286 (5.24%)	5 / 1461 (0.34%)
occurrences (all)	22	17	5
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	4 / 289 (1.38%)	39 / 286 (13.64%)	9 / 1461 (0.62%)
occurrences (all)	4	45	9
Dysuria			
subjects affected / exposed	17 / 289 (5.88%)	17 / 286 (5.94%)	4 / 1461 (0.27%)
occurrences (all)	20	22	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	69 / 289 (23.88%)	80 / 286 (27.97%)	47 / 1461 (3.22%)
occurrences (all)	85	99	55
Myalgia			
subjects affected / exposed	58 / 289 (20.07%)	67 / 286 (23.43%)	31 / 1461 (2.12%)
occurrences (all)	93	90	40
Bone pain			
subjects affected / exposed	39 / 289 (13.49%)	45 / 286 (15.73%)	24 / 1461 (1.64%)
occurrences (all)	49	49	33
Musculoskeletal pain			
subjects affected / exposed	27 / 289 (9.34%)	39 / 286 (13.64%)	15 / 1461 (1.03%)
occurrences (all)	38	40	16
Back pain			
subjects affected / exposed	29 / 289 (10.03%)	35 / 286 (12.24%)	15 / 1461 (1.03%)
occurrences (all)	37	36	15
Pain in extremity			
subjects affected / exposed	21 / 289 (7.27%)	38 / 286 (13.29%)	4 / 1461 (0.27%)
occurrences (all)	27	42	4
Muscle spasms			

subjects affected / exposed	16 / 289 (5.54%)	7 / 286 (2.45%)	2 / 1461 (0.14%)
occurrences (all)	18	8	3
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	39 / 289 (13.49%)	38 / 286 (13.29%)	24 / 1461 (1.64%)
occurrences (all)	46	43	24
Urinary tract infection			
subjects affected / exposed	22 / 289 (7.61%)	45 / 286 (15.73%)	24 / 1461 (1.64%)
occurrences (all)	24	55	30
Nasopharyngitis			
subjects affected / exposed	18 / 289 (6.23%)	29 / 286 (10.14%)	6 / 1461 (0.41%)
occurrences (all)	26	38	6
Rhinitis			
subjects affected / exposed	20 / 289 (6.92%)	27 / 286 (9.44%)	0 / 1461 (0.00%)
occurrences (all)	20	29	0
Infection			
subjects affected / exposed	8 / 289 (2.77%)	15 / 286 (5.24%)	12 / 1461 (0.82%)
occurrences (all)	8	16	13
Cystitis			
subjects affected / exposed	5 / 289 (1.73%)	16 / 286 (5.59%)	8 / 1461 (0.55%)
occurrences (all)	11	17	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	63 / 289 (21.80%)	63 / 286 (22.03%)	13 / 1461 (0.89%)
occurrences (all)	71	75	16
Hyperglycaemia			
subjects affected / exposed	14 / 289 (4.84%)	19 / 286 (6.64%)	13 / 1461 (0.89%)
occurrences (all)	16	23	13
Hypokalaemia			
subjects affected / exposed	17 / 289 (5.88%)	13 / 286 (4.55%)	27 / 1461 (1.85%)
occurrences (all)	18	13	30
Dehydration			
subjects affected / exposed	13 / 289 (4.50%)	15 / 286 (5.24%)	4 / 1461 (0.27%)
occurrences (all)	17	15	4

Non-serious adverse events	Safety Cohort 2: Chemo + Trastuzumab +	Chemotherapy + Trastuzumab (>18 months)	Chemotherapy + Trastuzumab + Bevacizumab (>18

	Bevacizumab(<18 months)		months)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	989 / 1436 (68.87%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	20 / 1436 (1.39%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	21	0	0
Lymphoedema			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	3	0	0
Flushing			
subjects affected / exposed	5 / 1436 (0.35%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	5	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	103 / 1436 (7.17%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	149	0	0
Mucosal inflammation			
subjects affected / exposed	51 / 1436 (3.55%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	57	0	0
Asthenia			
subjects affected / exposed	52 / 1436 (3.62%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	58	0	0
Pyrexia			
subjects affected / exposed	18 / 1436 (1.25%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	19	0	0
Oedema peripheral			
subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	4	0	0
Oedema			
subjects affected / exposed	0 / 1436 (0.00%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	1 / 1436 (0.07%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	31 / 1436 (2.16%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	35	0	0
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	97 / 1436 (6.75%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	98	0	0
Breast pain			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	83 / 1436 (5.78%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	100	0	0
Cough			
subjects affected / exposed	10 / 1436 (0.70%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	11	0	0
Dyspnoea			
subjects affected / exposed	12 / 1436 (0.84%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	14	0	0
Oropharyngeal pain			
subjects affected / exposed	6 / 1436 (0.42%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	7	0	0
Respiratory tract haemorrhage			
subjects affected / exposed	9 / 1436 (0.63%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	10	0	0
Dysphonia			
subjects affected / exposed	5 / 1436 (0.35%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	6	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 1436 (0.63%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	9	0	0
Anxiety			
subjects affected / exposed	5 / 1436 (0.35%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	5	0	0

Depression			
subjects affected / exposed	6 / 1436 (0.42%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	6	0	0
Investigations			
Weight decreased			
subjects affected / exposed	10 / 1436 (0.70%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	11	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	29 / 1436 (2.02%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	35	0	0
Alanine aminotransferase increased			
subjects affected / exposed	14 / 1436 (0.97%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	19	0	0
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	12 / 1436 (0.84%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	13	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 1436 (2.09%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	34	0	0
Dysgeusia			
subjects affected / exposed	6 / 1436 (0.42%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	6	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	80 / 1436 (5.57%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	83	0	0
Dizziness			
subjects affected / exposed	9 / 1436 (0.63%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	9	0	0
Neuropathy peripheral			
subjects affected / exposed	41 / 1436 (2.86%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	44	0	0
Paraesthesia			
subjects affected / exposed	11 / 1436 (0.77%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	12	0	0

Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	315 / 1436 (21.94%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	604	0	0
Anaemia			
subjects affected / exposed	127 / 1436 (8.84%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	134	0	0
Leukopenia			
subjects affected / exposed	101 / 1436 (7.03%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	175	0	0
Thrombocytopenia			
subjects affected / exposed	135 / 1436 (9.40%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	174	0	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	14 / 1436 (0.97%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	15	0	0
Vision blurred			
subjects affected / exposed	2 / 1436 (0.14%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	95 / 1436 (6.62%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	118	0	0
Diarrhoea			
subjects affected / exposed	148 / 1436 (10.31%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	175	0	0
Vomiting			
subjects affected / exposed	56 / 1436 (3.90%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	66	0	0
Constipation			
subjects affected / exposed	25 / 1436 (1.74%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	28	0	0
Stomatitis			
subjects affected / exposed	46 / 1436 (3.20%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	53	0	0

Dyspepsia			
subjects affected / exposed	13 / 1436 (0.91%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	13	0	0
Abdominal pain			
subjects affected / exposed	22 / 1436 (1.53%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	22	0	0
Abdominal pain upper			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	3	0	0
Haemorrhoids			
subjects affected / exposed	16 / 1436 (1.11%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	16	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	91 / 1436 (6.34%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	93	0	0
Nail disorder			
subjects affected / exposed	15 / 1436 (1.04%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	15	0	0
Rash			
subjects affected / exposed	21 / 1436 (1.46%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	23	0	0
Dry skin			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	3	0	0
Pruritus			
subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	5	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	12 / 1436 (0.84%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	13	0	0
Erythema			
subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	5	0	0
Renal and urinary disorders			

Proteinuria			
subjects affected / exposed	94 / 1436 (6.55%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	111	0	0
Dysuria			
subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	4	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	56 / 1436 (3.90%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	58	0	0
Myalgia			
subjects affected / exposed	19 / 1436 (1.32%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	21	0	0
Bone pain			
subjects affected / exposed	20 / 1436 (1.39%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	21	0	0
Musculoskeletal pain			
subjects affected / exposed	31 / 1436 (2.16%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	35	0	0
Back pain			
subjects affected / exposed	10 / 1436 (0.70%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	12	0	0
Pain in extremity			
subjects affected / exposed	16 / 1436 (1.11%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	18	0	0
Muscle spasms			
subjects affected / exposed	3 / 1436 (0.21%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	19 / 1436 (1.32%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	20	0	0
Urinary tract infection			
subjects affected / exposed	28 / 1436 (1.95%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	29	0	0
Nasopharyngitis			

subjects affected / exposed	10 / 1436 (0.70%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	10	0	0
Rhinitis			
subjects affected / exposed	4 / 1436 (0.28%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	4	0	0
Infection			
subjects affected / exposed	16 / 1436 (1.11%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	19	0	0
Cystitis			
subjects affected / exposed	5 / 1436 (0.35%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	5	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 1436 (1.11%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	19	0	0
Hyperglycaemia			
subjects affected / exposed	10 / 1436 (0.70%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	10	0	0
Hypokalaemia			
subjects affected / exposed	19 / 1436 (1.32%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	21	0	0
Dehydration			
subjects affected / exposed	13 / 1436 (0.91%)	0 / 1750 (0.00%)	0 / 1722 (0.00%)
occurrences (all)	14	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was terminated prematurely as there were no efficacy benefits accrued to participants with use of bevacizumab and there were no new safety concerns found when examining the study data.

Notes: