Clinical trial results:
A Randomized Multicenter, Double-Blind, Placebo-Controlled Comparison of Chemotherapy Plus Trastuzumab Plus Placebo Versus Chemotherapy Plus Trastuzumab Plus Pertuzumab as Adjuvant Therapy in Patients with Operable HER2-Positive Primary Breast Cancer

Summary

EudraCT number	2010-022902-41
Trial protocol	GB HU CZ ES FR IE SE DK SI NL BE SK AT IT BG
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	22 December 2017
First version publication date	22 December 2017

Trial information

Trial identification

Sponsor protocol code	BO25126

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01358877
WHO universal trial number (UTN)	-
Other trial identifiers	Genentech protocol code: TOC4939g, Breast International Group: BIG 4-11

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	Interim
Date of interim/final analysis	19 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare invasive disease-free survival (IDFS) (excluding second non breast cancers) in participants with human epidermal growth receptor 2 (HER2)-positive early breast cancer randomized to chemotherapy plus 1 year of trastuzumab plus placebo, or chemotherapy plus 1 year of trastuzumab plus pertuzumab.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol. Approval from the Institutional Review Board (IRB)/Ethics Committees (ECs) was obtained before study start. The sponsor also obtained approval from the relevant regulatory authorities prior to starting the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Australia: 109
Country: Number of subjects enrolled	Austria: 52
Country: Number of subjects enrolled	Belgium: 131
Country: Number of subjects enrolled	Bulgaria: 21
Country: Number of subjects enrolled	Canada: 110
Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	China: 372
Country: Number of subjects enrolled	Colombia: 13
Country: Number of subjects enrolled	Croatia: 15
Country: Number of subjects enrolled	Czech Republic: 26
Country: Number of subjects enrolled	Denmark: 87
Country: Number of subjects enrolled	El Salvador: 7
Country: Number of subjects enrolled	France: 544
Country: Number of subjects enrolled	Germany: 460
Country: Number of subjects enrolled	Guatemala: 12
Country: Number of subjects enrolled	Hong Kong: 16
Country: Number of subjects enrolled	Hungary: 63

Country: Number of subjects enrolled	Ireland: 43
Country: Number of subjects enrolled	Israel: 39
Country: Number of subjects enrolled	Italy: 255
Country: Number of subjects enrolled	Japan: 302
Country: Number of subjects enrolled	Mexico: 35
Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	New Zealand: 19
Country: Number of subjects enrolled	Panama: 15
Country: Number of subjects enrolled	Peru: 25
Country: Number of subjects enrolled	Philippines: 36
Country: Number of subjects enrolled	Poland: 110
Country: Number of subjects enrolled	Romania: 25
Country: Number of subjects enrolled	Russian Federation: 58
Country: Number of subjects enrolled	Slovenia: 9
Country: Number of subjects enrolled	South Africa: 21
Country: Number of subjects enrolled	Korea, Republic of: 136
Country: Number of subjects enrolled	Spain: 343
Country: Number of subjects enrolled	Sweden: 72
Country: Number of subjects enrolled	Switzerland: 50
Country: Number of subjects enrolled	Taiwan: 170
Country: Number of subjects enrolled	Thailand: 75
Country: Number of subjects enrolled	Ukraine: 73
Country: Number of subjects enrolled	United Kingdom: 224
Country: Number of subjects enrolled	United States: 590
Worldwide total number of subjects	4804
EEA total number of subjects	2504

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)	4196
From 65 to 84 years	605
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The analysis included data up to a clinical data cut-off date of 19 December 2016.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pertuzumab + Trastuzumab + Chemotherapy

Arm description:

Participants received pertuzumab (840 mg loading dose, then 420 mg) and trastuzumab (8 mg/kg loading dose, then 6 mg/kg) intravenously (IV) every 3 weeks (Q3W) for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m^2 + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 once weekly (QW); 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin area under the curve (AUC) 6 (up to 900 mg).

Arm type	Experimental
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	Perjeta®, rhuMAb 2C4
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab will be administered as per the schedule specified in the arm description.

Arm title	Placebo + Trastuzumab + Chemotherapy

Arm description:

Participants received placebo matched to pertuzumab IV Q3W and trastuzumab (8 milligrams per kilogram [mg/kg] loading dose, then 6 mg/kg) IV Q3W for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 milligrams per square meter (mg/m^2) + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin AUC 6 (up to 900 milligrams [mg]).

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo matched to pertuzumab will be administered as per the schedule specified in the arm.

Number of subjects in period 1	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy
Started	2400	2404
Completed	0	0
Not completed	2400	2404
Ongoing follow-up for overall survival	7	5
Ongoing follow-up for IDFS event	2084	2073
Death	80	89
Ongoing follow-up for post-recurrence	87	108
Unspecified	142	129

Baseline characteristics

Reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Chemotherapy

Reporting group description:

Participants received pertuzumab (840 mg loading dose, then 420 mg) and trastuzumab (8 mg/kg loading dose, then 6 mg/kg) intravenously (IV) every 3 weeks (Q3W) for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m^2 + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 once weekly (QW); 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin area under the curve (AUC) 6 (up to 900 mg).

Reporting group title	Placebo + Trastuzumab + Chemotherapy

Reporting group description:

Participants received placebo matched to pertuzumab IV Q3W and trastuzumab (8 milligrams per kilogram [mg/kg] loading dose, then 6 mg/kg) IV Q3W for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 milligrams per square meter (mg/m^2) + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin AUC 6 (up to 900 milligrams [mg]).

Reporting group values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy	Total
Number of subjects	2400	2404	4804
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	51.7	51.4	
standard deviation	± 10.9	± 10.7	-
Gender Categorical Units: Subjects			
Female	2397	2396	4793
Male	3	8	11

End points

End points reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Chemotherapy

Reporting group description:

Participants received pertuzumab (840 mg loading dose, then 420 mg) and trastuzumab (8 mg/kg loading dose, then 6 mg/kg) intravenously (IV) every 3 weeks (Q3W) for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m^2 + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 once weekly (QW); 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin area under the curve (AUC) 6 (up to 900 mg).

Reporting group title	Placebo + Trastuzumab + Chemotherapy

Reporting group description:

Participants received placebo matched to pertuzumab IV Q3W and trastuzumab (8 milligrams per kilogram [mg/kg] loading dose, then 6 mg/kg) IV Q3W for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 milligrams per square meter (mg/m^2) + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin AUC 6 (up to 900 milligrams [mg]).

Subject analysis set title	Pertuzumab + Trastuzumab + Chemotherapy
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received pertuzumab (840 mg loading dose, then 420 mg) and trastuzumab (8 mg/kg loading dose, then 6 mg/kg) IV Q3W for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m^2 + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin AUC 6 (up to 900 mg).

Subject analysis set title	Placebo + Trastuzumab + Chemotherapy
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received placebo matched to pertuzumab IV Q3W and trastuzumab (8 mg/kg loading dose, then 6 mg/kg) IV Q3W for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m^2 + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin AUC 6 (up to 900 mg).

Subject analysis set title	Pertuzumab + Trastuzumab + Chemotherapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received pertuzumab (840 mg loading dose, then 420 mg) and trastuzumab (8 mg/kg loading dose, then 6 mg/kg) IV Q3W for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m^2 + epirubicin 90-120 mg/m^2 or

doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin AUC 6 (up to 900 mg).

Subject analysis set title	Placebo + Trastuzumab + Chemotherapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received placebo matched to pertuzumab IV Q3W and trastuzumab (8 mg/kg loading dose, then 6 mg/kg) IV Q3W for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m^2 + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin AUC 6 (up to 900 mg).

Primary: Percentage of Participants With IDFS Event (Excluding Second Primary Non-Breast Cancer [SPNBC]), as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point title	Percentage of Participants With IDFS Event (Excluding Second Primary Non-Breast Cancer [SPNBC]), as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point description:

Percentage of participants with IDFS events (excluding SPNBC) is reported. IDFS event was defined as the first occurrence of one of the following events: Ipsilateral invasive breast tumor recurrence (that is [i.e.], an invasive breast cancer involving the same breast parenchyma as the original primary lesion); ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast); distant recurrence (i.e., evidence of breast cancer in any anatomic site - other than the two above mentioned sites); death attributable to any cause; contralateral invasive breast cancer. All SPNBCs and in situ carcinomas (including ductal carcinoma in situ [DCIS] and lobular carcinoma in situ [LCIS]) and non-melanoma skin cancer were excluded as an event. Intent-to-treat (ITT) population included all randomized participants regardless of treatment received.

End point type	Primary

End point timeframe:

Randomization to the first occurrence of IDFS event (excluding SPNBC) (until data cut-off date 19 December 2016, up to maximum length of follow-up of 59 months)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)	7.1	8.7		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using stratified log-rank test, which included nodal status, protocol version,

central hormone receptor status, and adjuvant chemotherapy regimen as stratification factors in the randomization. Hazard ratios were estimated by Cox regression.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4804
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0446 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1

Notes:

[1] - Statistical significance was controlled at a two-sided alpha level of 0.05.

Primary: Kaplan-Meier Estimate of the Percentage of Participants Who Were IDFS Event-Free (Excluding SPNBC) at Year 3, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were IDFS Event-Free (Excluding SPNBC) at Year 3, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings[2]

End point description:

Kaplan-Meier estimate of the percentage of participants who were IDFS event-free (excluding SPNBC) at Year 3 is reported. IDFS event the first occurrence of one of the following events: Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion); ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast); distant recurrence (i.e., evidence of breast cancer in any anatomic site - other than the two above mentioned sites); death attributable to any cause; contralateral invasive breast cancer. All SPNBCs and in situ carcinomas (including DCIS and LCIS) and non-melanoma skin cancer were excluded as an event. ITT population. Number of subjects analysed = participants remaining at risk for IDFS event (excluding SPNBC) at Year 3.

End point type	Primary

End point timeframe:

3 years

Notes:

[2] - 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: The primary outcome measure was analyzed for a relative treatment difference using the hazard ratio and log-rank test. Kaplan-Meier 3-year estimates of the primary outcome measure are only presented as additional descriptive summary statistics.

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2101	2108		
Units: estimate of percentage of participants				
number (confidence interval 95%)	94.06 (93.09 to 95.03)	93.24 (92.21 to 94.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With IDFS Event (Including SPNBC), as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point title	Percentage of Participants With IDFS Event (Including SPNBC), as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point description:

Percentage of participants with IDFS events (including SPNBC) is reported. IDFS-SPNBC event was defined as the first occurrence of one of the following events: Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion); ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast); distant recurrence (i.e., evidence of breast cancer in any anatomic site - other than the two above mentioned sites); death attributable to any cause; contralateral invasive breast cancer; SPNBC (with the exception of non-melanoma skin cancers and in situ carcinoma of any site). ITT population.

End point type	Secondary

End point timeframe:

Randomization to the first occurrence of IDFS event (including SPNBC) (until data cut-off date 19 December 2016, up to maximum length of follow-up of 59 months)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)	7.9	9.6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using stratified log-rank test, which included nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen as stratification factors in the randomization. Hazard ratios were estimated by Cox regression.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy

Number of subjects included in analysis	4804
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.99

Notes:

[3] - Statistical significance was controlled at a two-sided alpha level of 0.05.

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Were IDFS Event-Free (Including SPNBC) at Year 3, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were IDFS Event-Free (Including SPNBC) at Year 3, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point description:

Kaplan-Meier estimate of the percentage of participants who were IDFS event-free (including SPNBC) at Year 3 is reported. IDFS-SPNBC event was defined as the first occurrence of one of the following events: Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion); ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast); distant recurrence (i.e., evidence of breast cancer in any anatomic site - other than the two above mentioned sites); death attributable to any cause; contralateral invasive breast cancer; SPNBC (with the exception of non-melanoma skin cancers and in situ carcinoma of any site). ITT population. Number of subjects analysed = participants remaining at risk for IDFS event (including SPNBC) at Year 3.

End point type	Secondary

End point timeframe:

3 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2093	2095		
Units: estimate of percentage of participants				
number (confidence interval 95%)	93.50 (92.49 to 94.51)	92.51 (91.43 to 93.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Disease-Free Survival (DFS) Event, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point title	Percentage of Participants With Disease-Free Survival (DFS) Event, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point description:

Percentage of participants with DFS event is reported. DFS event was defined as the first occurrence of one of the following events: Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion); ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast); distant recurrence (i.e., evidence of breast cancer in any anatomic site - other than the two above mentioned sites); death attributable to any cause; contralateral invasive breast cancer; SPNBC or contralateral or ipsilateral DCIS. ITT population.

End point type	Secondary

End point timeframe:

Randomization to the first occurrence of DFS event (until data cut-off date 19 December 2016, up to maximum length of follow-up of 59 months)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)	8.0	9.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using stratified log-rank test, which included nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen as stratification factors in the randomization. Hazard ratios were estimated by Cox regression.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4804
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0327 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.98

Notes:

[4] - Statistical significance was controlled at a two-sided alpha level of 0.05.

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Were DFS Event-Free at Year 3, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were DFS Event-Free at Year 3, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point description:

Kaplan-Meier estimate of the percentage of participants who were DFS event-free at Year 3 is reported. DFS event was defined as the first occurrence of one of the following events: Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion); ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast); distant recurrence (i.e., evidence of breast cancer in any anatomic site - other than the two above mentioned sites); death attributable to any cause; contralateral invasive breast cancer; SPNBC or contralateral or ipsilateral DCIS. ITT population. Number of subjects analysed = participants remaining at risk for DFS event at Year 3.

End point type	Secondary

End point timeframe:

3 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2091	2090		
Units: estimate of percentage of participants				
number (confidence interval 95%)	93.42 (92.40 to 94.43)	92.29 (91.21 to 93.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

Percentage of participants who died due to any cause is reported. ITT population.

End point type	Secondary

End point timeframe:

Randomization until death due to any cause (until data cut-off date 19 December 2016, up to maximum length of follow-up of 59 months)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)	3.3	3.7		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using stratified log-rank test, which included nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen as stratification factors in the randomization. Hazard ratios were estimated by Cox regression.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4804
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4673 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.21

Notes:

[5] - Statistical significance was controlled at a two-sided alpha level of 0.05.

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Were Alive at Year 3

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were Alive at Year 3

End point description:

The Kaplan-Meier approach was used to estimate the percentage of participants who were alive at 3 years. ITT population. Number of subjects analysed = participants remaining at risk for death at Year 3.

End point type	Secondary

End point timeframe:

3 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2186	2209		
Units: estimate of percentage of participants				
number (confidence interval 95%)	97.65 (97.03 to 98.27)	97.67 (97.06 to 98.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Recurrence-Free Interval (RFI) Event, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point title	Percentage of Participants With Recurrence-Free Interval (RFI) Event, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point description:

Percentage of participants with RFI event is reported. RFI event was defined as local, regional or distant breast cancer recurrence. ITT population.

End point type	Secondary

End point timeframe:

Randomization until local, regional or distant breast cancer recurrence (until data cut-off date 19 December 2016, up to maximum length of follow-up of 59 months)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)	5.8	7.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using stratified log-rank test, which included nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen as stratification factors in the randomization. Hazard ratio were estimated by Cox regression.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy

Number of subjects included in analysis	4804
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.99

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Were RFI Event-Free at Year 3, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were RFI Event-Free at Year 3, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point description:

Kaplan-Meier estimate of the percentage of participants who were RFI event-free at Year 3 is reported. RFI event was defined local, regional or distant breast cancer recurrence. ITT population. Number of subjects analysed = participants remaining at risk for RFI event at Year 3.

End point type	Secondary

End point timeframe:

3 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2116	2129		
Units: estimate of percentage of participants				
number (confidence interval 95%)	95.18 (94.30 to 96.06)	94.27 (93.32 to 95.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Distant Recurrence-Free Interval (DRFI) Event, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point title	Percentage of Participants With Distant Recurrence-Free Interval (DRFI) Event, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point description:

Percentage of participants with DRFI event is reported. DRFI event was defined as distant breast cancer recurrence. ITT population.

End point type	Secondary

End point timeframe:

Randomization until distant breast cancer recurrence (until data cut-off date 19 December 2016, up to maximum length of follow-up of 59 months)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)	5.0	6.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using stratified log-rank test, which included nodal status, protocol version, central hormone receptor status, and adjuvant chemotherapy regimen as stratification factors in the randomization. Hazard ratio were estimated by Cox regression.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4804
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1007
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.04

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Were DRFI Event-Free at Year 3, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were DRFI Event-Free at Year 3, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings

End point description:

Kaplan-Meier estimate of the percentage of participants who were DRFI event-free at Year 3 is reported. DRFI event was defined as distant breast cancer recurrence. ITT population. Number of subjects analysed = participants remaining at risk for DRFI event at Year 3.

End point type	Secondary

End point timeframe:

3 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2126	2145		
Units: estimate of percentage of participants				
number (confidence interval 95%)	95.70 (94.86 to 96.53)	95.13 (94.25 to 96.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Primary Cardiac Event

End point title	Percentage of Participants With Primary Cardiac Event

End point description:

Primary cardiac event was defined as either: Heart Failure (New York Heart Association [NYHA] Class III or IV) and a drop in left ventricular ejection fraction (LVEF) of at least 10 ejection fraction (EF) points from baseline and to below 50 percent (%); or cardiac death. Cardiac death was defined as either definite cardiac death: due to heart failure, myocardial infarction, or documented primary arrhythmia; or probable cardiac death: sudden unexpected death within 24 hours of a definite or probable cardiac event (e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia) without documented etiology. Safety population included participants who received any amount of study medication (chemotherapy, pertuzumab/placebo, or trastuzumab), according to the treatment actually received.

End point type	Secondary

End point timeframe:

Baseline until data cut-off date 19 December 2016 (up to maximum length of follow-up of 59 months)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2364	2405		
Units: percentage of participants				
number (not applicable)				
Primary Cardiac Event (Composite)	0.7	0.3		
Heart Failure and LVEF decline	0.6	0.2		
Cardiac Death (Definite or Probable)	0.1	0.1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The difference in percentage of participants with a primary cardiac event between the pertuzumab and placebo arms. The 95% confidence interval (CI) was estimated using Hauck-Anderson correction.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.8

Secondary: Percentage of Participants With Secondary Cardiac Event

End point title	Percentage of Participants With Secondary Cardiac Event

End point description:

Secondary cardiac event was defined as asymptomatic or mildly symptomatic (NYHA Class II) significant drop in LVEF (defined as an absolute decrease of at least 10 EF points from baseline and to below 50%), confirmed by a second LVEF assessment within approximately three weeks of the first significant LVEF assessment or confirmed by the Cardiac Advisory Board (CAB). Safety population.

End point type	Secondary

End point timeframe:

Baseline until data cut-off date 19 December 2016 (up to maximum length of follow-up of 59 months)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2364	2405		
Units: percentage of participants				
number (not applicable)	2.7	2.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

95% CI was estimated using Hauck-Anderson correction.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy

Number of subjects included in analysis	4769
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.9

Secondary: Change From Baseline in LVEF to Worst Post-Baseline Value

End point title	Change From Baseline in LVEF to Worst Post-Baseline Value

End point description:

LVEF is the fraction of blood (in percent) pumped out of the heart's left ventricular chamber with each heart beat, and is a measure of cardiac output for the heart. Baseline LVEF value and the maximum absolute decrease (worst value) in LVEF measurement from baseline were reported. LVEF was measured by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan. Safety population. "Number of subjects analysed"=participants evaluable for this endpoint. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline until data cut-off date 19 December 2016 (up to maximum length of follow-up of 59 months)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2363	2401		
Units: percentage of blood pumped out				
arithmetic mean (standard deviation)				
Baseline (n=2363, 2401)	65.2 (± 5.9)	65.3 (± 6.1)		
Change to Worst Value (n=2348, 2351)	-7.5 (± 6.6)	-7.6 (± 6.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

95% CI was estimated using Hauck-Anderson correction.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy

Number of subjects included in analysis	4764
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Treatment Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.5

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) Global Health Status (GHS) Scale Score

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) Global Health Status (GHS) Scale Score

End point description:

EORTC QLQ-C30 is a cancer-specific instrument with 30 questions used to assess overall quality of life(QOL)in cancer participants. First 28 questions used 4-point scale(1=not at all,2=a little,3=quite a bit,4=very much)for evaluating 5 functional scales(physical, role, social, cognitive, emotional),8 symptom scales(diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea and vomiting[N/V], constipation, pain) and a single item (financial difficulties). Last 2 questions represented participant's assessment of overall health and quality of life, used 7-point scale(1=very poor to 7=excellent). Global scores were linearly transformed on a scale of 0 to 100, with a high score indicating better GHS/QOL. Negative change from Baseline values indicated deterioration in QOL or functioning. ITT population. "Number of subjects analysed"=participants evaluable for this endpoint. n= participants responding to this scale where it is considered complete as defined by EORTC QLQ-C30 scoring manual.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; end of treatment (EOT, 28 days after the last dose, up to Week 56); Follow-up (FU) Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2329	2338		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=2329, 2338)	72.9 (± 19.7)	72.5 (± 19.7)		
Change at Week 13 (n=2065, 2110)	-11.2 (± 22.8)	-10.2 (± 22.6)		
Change at Week 25 (n=2035, 2073)	-4.4 (± 21.6)	-2.9 (± 21.0)		
Change at EOT (n=2254, 2282)	-3.1 (± 21.9)	-1.1 (± 21.8)		
Change at FU Month 18 (n=1906, 1918)	1.9 (± 21.5)	1.3 (± 22.2)		
Change at FU Month 24 (n=1861, 1866)	2.2 (± 22.1)	2.4 (± 22.1)		
Change at FU Month 36 (n=1811, 1782)	2.8 (± 21.4)	1.8 (± 22.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EORTC QLQ-C30 Functioning Subscale Scores

End point title	Change From Baseline in EORTC QLQ-C30 Functioning Subscale Scores

End point description:

EORTC QLQ-C30 is a cancer-specific instrument with 30 questions used to assess overall QOL in cancer participants. First 28 questions used 4-point scale (1=not at all,2=a little,3=quite a bit,4=very much) for evaluating 5 functional scales (physical, role, social, cognitive, emotional), 8 symptom scales (diarrhea, fatigue, dyspnea, appetite loss, insomnia, N/V, constipation, and pain) and a single item (financial difficulties). Last 2 questions represented participant's assessment of overall health and quality of life, coded on 7-point scale(1=very poor to 7=excellent). EORTC QLQ-C30 functioning scores were linearly transformed on a scale of 0 to 100, with a high score indicating better functioning/support. Negative change from Baseline values indicated deterioration in functioning. ITT population. "Number of subjects analysed"=participants evaluable for this endpoint. n= participants responding to this scale where it is considered complete as defined by EORTC QLQ-C30 scoring manual.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; EOT (28 days after the last dose, up to Week 56); FU Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2338	2342		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=2338, 2342): Physical	89.6 (± 12.9)	89.1 (± 13.4)		
Change at Week 13 (n=2077, 2115): Physical	-10.7 (± 17.2)	-10.6 (± 17.7)		
Change at Week 25 (n=2052, 2078): Physical	-4.6 (± 14.5)	-4.3 (± 14.5)		
Change at EOT (n=2262, 2287): Physical	-4.1 (± 14.7)	-3.2 (± 14.9)		
Change at FU Month 18 (n=1918, 1925): Physical	-0.9 (± 13.5)	-0.9 (± 14.5)		
Change at FU Month 24 (n=1867, 1875): Physical	-0.4 (± 13.8)	-0.3 (± 14.5)		
Change at FU Month 36 (n=1820, 1792): Physical	-0.3 (± 14.1)	-0.1 (± 13.9)		
Baseline (n=2334, 2337): Role	79.8 (± 24.7)	79.4 (± 25.2)		
Change at Week 13 (n=2075, 2111): Role	-8.0 (± 28.6)	-8.5 (± 29.5)		
Change at Week 25 (n=2049, 2073): Role	-0.7 (± 26.4)	0.4 (± 27.8)		
Change at EOT (n=2258, 2281): Role	0.4 (± 27.8)	2.3 (± 28.1)		
Change at FU Month 18 (n=1916, 1921): Role	6.1 (± 26.5)	5.7 (± 28.9)		
Change at FU Month 24 (n=1865, 1872): Role	7.3 (± 26.8)	6.9 (± 28.2)		
Change at FU Month 36 (n=1817, 1790): Role	7.9 (± 26.4)	7.6 (± 27.9)		
Baseline (n=2332, 2336): Social	81.9 (± 22.9)	80.6 (± 24.1)		

Change at Week 13 (n=2071, 2110): Social	-8.7 (± 25.8)	-7.8 (± 27.1)		
Change at Week 25 (n=2044, 2072): Social	-2.2 (± 24.5)	-0.7 (± 26.3)		
Change at EOT (n=2258, 2282): Social	0.0 (± 25.2)	1.2 (± 26.3)		
Change at FU Month 18 (n=1910, 1915): Social	5.0 (± 23.8)	4.8 (± 26.7)		
Change at FU Month 24 (n=1864, 1868): Social	5.5 (± 24.8)	6.5 (± 26.6)		
Change at FU Month 36 (n=1812, 1783): Social	6.6 (± 24.9)	7.1 (± 27.3)		
Baseline (n=2334, 2341): Cognitive	88.8 (± 16.6)	87.9 (± 17.9)		
Change at Week 13 (n=2073, 2115): Cognitive	-9.1 (± 20.5)	-9.0 (± 21.4)		
Change at Week 25 (n=2046, 2076): Cognitive	-7.6 (± 20.4)	-7.0 (± 20.8)		
Change at EOT (n=2259, 2287): Cognitive	-7.7 (± 20.6)	-7.2 (± 21.4)		
Change at FU Month 18 (n=1911, 1920): Cognitive	-6.1 (± 19.6)	-5.8 (± 21.2)		
Change at FU Month 24 (n=1865, 1870): Cognitive	-6.2 (± 20.5)	-5.5 (± 21.7)		
Change at FU Month 36 (n=1814, 1786): Cognitive	-5.4 (± 20.6)	-4.9 (± 21.8)		
Baseline (n=2332, 2340): Emotional	72.8 (± 22.4)	71.3 (± 22.7)		
Change at Week 13 (n=2071, 2114): Emotional	3.3 (± 22.2)	2.9 (± 22.5)		
Change at Week 25 (n=2044, 2076): Emotional	5.1 (± 22.7)	5.9 (± 22.2)		
Change at EOT (n=2257, 2286): Emotional	5.6 (± 23.2)	6.2 (± 23.4)		
Change at FU Month 18 (n=1909, 1918): Emotional	7.7 (± 23.4)	7.6 (± 23.4)		
Change at FU Month 24 (n=1864, 1869): Emotional	7.8 (± 23.3)	8.5 (± 24.2)		
Change at FU Month 36 (n=1812, 1785): Emotional	7.8 (± 23.8)	8.4 (± 24.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EORTC QLQ-C30 Disease/Treatment-Related Symptoms Subscale Scores

End point title	Change From Baseline in EORTC QLQ-C30 Disease/Treatment-Related Symptoms Subscale Scores

End point description:

EORTC QLQ-C30 is a cancer-specific instrument with 30 questions used to assess overall QOL in cancer participants. First 28 questions used 4-point scale(1=not at all,2=a little,3=quite a bit,4=very much)for evaluating 5 functional scales (physical,role,social,cognitive,emotional), 8 symptom scales(diarrhea,fatigue,dyspnea,appetite loss,insomnia,nausea and vomiting[N/V],constipation,pain)and a single item(financial difficulties). Last 2 questions represented participant's assessment of overall health and QOL, coded on 7-point scale(1=very poor to 7=excellent). EORTC QLQ-C30 disease/treatment-related symptom scores were linearly transformed on scale of 0 to 100, with high score indicating higher level of symptoms. Negative change from Baseline values indicated improvement in symptoms. ITT population. "Number of subjects analysed"=participants evaluable for this endpoint. n= participants responding to this scale where it is considered complete as defined by EORTC QLQ-C30

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; EOT (28 days after the last dose, up to Week 56); FU Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2338	2342		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=2329, 2339):Diarrhea	5.2 (± 14.4)	5.1 (± 13.5)		
Change at Week 13 (n=2067, 2111):Diarrhea	22.3 (± 29.8)	9.2 (± 23.9)		
Change at Week 25 (n=2043, 2075):Diarrhea	13.2 (± 26.5)	3.3 (± 19.8)		
Change at EOT (n=2257, 2285):Diarrhea	12.2 (± 26.9)	2.9 (± 20.0)		
Change at FU Month 18 (n=1907, 1919):Diarrhea	-0.5 (± 17.7)	0.2 (± 17.5)		
Change at FU Month 24 (n=1861, 1868):Diarrhea	-0.8 (± 17.4)	0.2 (± 18.3)		
Change at FU Month 36 (n=1810, 1784):Diarrhea	-0.8 (± 16.5)	0.3 (± 16.9)		
Baseline (n=2335, 2341):Fatigue	22.4 (± 19.7)	23.2 (± 20.5)		
Change at Week 13 (n=2074, 2116):Fatigue	16.1 (± 24.3)	16.2 (± 24.4)		
Change at Week 25 (n=2050, 2078):Fatigue	7.8 (± 22.5)	6.6 (± 22.3)		
Change at EOT (n=2259, 2287):Fatigue	7.1 (± 23.0)	5.2 (± 23.0)		
Change at FU Month 18 (n=1914, 1924):Fatigue	1.1 (± 21.7)	1.2 (± 22.5)		
Change at FU Month 24 (n=1864, 1873):Fatigue	0.4 (± 22.0)	0.4 (± 22.6)		
Change at FU Month 36 (n=1817, 1791):Fatigue	-0.2 (± 21.8)	0.6 (± 22.8)		
Baseline (n=2331, 2336):Dyspnea	6.8 (± 15.5)	8.0 (± 17.1)		
Change at Week 13 (n=2067, 2112):Dyspnea	12.3 (± 23.8)	14.6 (± 26.4)		
Change at Week 25 (n=2045, 2073):Dyspnea	6.3 (± 19.9)	6.4 (± 22.1)		
Change at EOT (n=2254, 2283):Dyspnea	6.6 (± 20.5)	6.5 (± 22.5)		
Change at FU Month 18 (n=1911, 1917):Dyspnea	5.9 (± 21.0)	5.0 (± 21.5)		
Change at FU Month 24 (n=1860, 1870):Dyspnea	5.1 (± 20.5)	5.3 (± 22.4)		
Change at FU Month 36 (n=1814, 1783):Dyspnea	5.1 (± 20.5)	5.3 (± 22.3)		
Baseline (n=2335, 2340):Appetite Loss	8.5 (± 18.2)	9.1 (± 18.7)		
Change at Week 13 (n=2073, 2114):Appetite Loss	13.6 (± 29.2)	7.7 (± 27.9)		
Change at Week 25 (n=2049, 2078):Appetite Loss	5.2 (± 25.1)	0.3 (± 22.4)		
Change at EOT (n=2257,2286):Appetite Loss	3.0 (± 24.5)	-0.9 (± 22.6)		

Change at FU Month 18 (n=1913, 1924):Appetite Loss	-3.0 (± 20.1)	-3.1 (± 21.1)		
Change at FU Month 24 (n=1862, 1871):Appetite Loss	-3.2 (± 20.6)	-3.3 (± 21.0)		
Change at FU Month 36 (n=1817, 1789):Appetite Loss	-3.0 (± 20.4)	-2.7 (± 21.2)		
Baseline (n=2333, 2338):Insomnia	25.3 (± 27.4)	27.3 (± 28.5)		
Change at Week 13 (n=2073, 2111):Insomnia	6.3 (± 30.3)	5.1 (± 32.2)		
Change at Week 25 (n=2049, 2073):Insomnia	4.3 (± 30.6)	2.0 (± 31.8)		
Change at EOT (n=2257, 2282):Insomnia	3.2 (± 31.0)	0.9 (± 32.8)		
Change at FU Month 18 (n=1913, 1917):Insomnia	-0.1 (± 31.1)	0.4 (± 32.4)		
Change at FU Month 24 (n=1863, 1869):Insomnia	-1.5 (± 31.3)	-1.1 (± 32.9)		
Change at FU Month 36 (n=1816, 1786):Insomnia	-0.3 (± 31.1)	-0.5 (± 33.5)		
Baseline (n=2338, 2342):N/V	2.7 (± 8.2)	3.1 (± 9.4)		
Change at Week 13 (n=2077, 2118):N/V	5.6 (± 15.7)	3.7 (± 14.5)		
Change at Week 25 (n=2052, 2079):N/V	1.1 (± 11.8)	0.5 (± 12.4)		
Change at EOT (n=2261, 2288):N/V	1.6 (± 12.7)	0.8 (± 13.2)		
Change at FU Month 18 (n=1918, 1925):N/V	-0.2 (± 10.5)	-0.4 (± 12.1)		
Change at FU Month 24 (n=1865, 1874):N/V	0.0 (± 10.7)	-0.1 (± 11.8)		
Change at FU Month 36 (n=1819, 1792):N/V	0.3 (± 11.0)	0.2 (± 11.7)		
Baseline (n=2335, 2339):Constipation	8.7 (± 19.1)	10.0 (± 19.8)		
Change at Week 13 (n=2066, 2113):Constipation	1.4 (± 23.5)	4.1 (± 25.6)		
Change at Week 25 (n=2047, 2075):Constipation	-0.7 (± 21.8)	0.2 (± 22.8)		
Change at EOT (n=2256,2285):Constipation	0.1 (± 22.4)	0.9 (± 23.3)		
Change at FU Month 18 (n=1912, 1922):Constipation	3.0 (± 23.3)	1.5 (± 23.8)		
Change at FU Month 24 (n=1865, 1872):Constipation	2.1 (± 23.1)	0.6 (± 22.9)		
Change at FU Month 36 (n=1815, 1784):Constipation	2.1 (± 22.9)	1.5 (± 22.7)		
Baseline (n=2337, 2342):Pain	18.8 (± 21.4)	19.6 (± 22.1)		
Change at Week 13 (n=2077, 2118):Pain	2.3 (± 25.4)	5.0 (± 26.1)		
Change at Week 25 (n=2051, 2080):Pain	1.4 (± 24.1)	1.4 (± 24.9)		
Change at EOT (n=2261, 2288):Pain	0.1 (± 24.7)	0.5 (± 25.8)		
Change at FU Month 18 (n=1918, 1927):Pain	-1.3 (± 23.3)	-0.5 (± 25.8)		
Change at FU Month 24 (n=1868, 1874):Pain	-1.6 (± 24.2)	-2.2 (± 25.6)		
Change at FU Month 36 (n=1818, 1792):Pain	-2.6 (± 24.4)	-2.3 (± 25.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EORTC QLQ-C30 Financial Difficulties Subscale Scores

End point title	Change From Baseline in EORTC QLQ-C30 Financial Difficulties Subscale Scores

End point description:

EORTC QLQ-C30 is a cancer-specific instrument with 30 questions used to assess overall QOL in cancer participants. First 28 questions used 4-point scale(1=not at all,2=a little,3=quite a bit,4=very much)for evaluating 5 functional scales (physical,role,social,cognitive,emotional), 8 symptom scales(diarrhea fatigue,dyspnea,appetite loss,insomnia,N/V,constipation,pain)and a single item(financial difficulties). Last 2 questions represented participant's assessment of overall health and quality of life, coded on 7-point scale(1=very poor to 7=excellent). Financial difficulties scores were linearly transformed on a scale of 0 and 100, with a high score indicating a higher level of financial difficulties. Negative change from Baseline values indicated improvement in financial difficulties. ITT population."Number of subjects analysed"=participants evaluable for this endpoint. n= participants responding to this scale where it is considered complete as defined by EORTC QLQ-C30 scoring manual.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; EOT (28 days after the last dose, up to Week 56); FU Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2319	2334		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=2319, 2334)	20.3 (± 28.7)	22.1 (± 30.0)		
Change at Week 13 (n=2052, 2103)	3.1 (± 26.1)	1.7 (± 27.0)		
Change at Week 25 (n=2025, 2067)	2.3 (± 26.8)	-0.3 (± 26.9)		
Change at EOT (n=2244, 2280)	-0.2 (± 27.6)	-1.5 (± 27.2)		
Change at FU Month 18 (n=1894, 1912)	-4.1 (± 27.9)	-5.1 (± 27.5)		
Change at FU Month 24 (n=1852, 1866)	-5.2 (± 28.6)	-6.9 (± 29.3)		
Change at FU Month 36 (n=1798, 1781)	-7.1 (± 28.5)	-8.3 (± 28.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organisation for Research and Treatment of Cancer - Breast Cancer Module Quality of Life (EORTC QLQ-BR23) Functional Scale Score

End point title	Change From Baseline in European Organisation for Research and Treatment of Cancer - Breast Cancer Module Quality of Life (EORTC QLQ-BR23) Functional Scale Score

End point description:

EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of four functional scales (body image, sexual enjoyment, sexual functioning, future perspective [FP]) and four symptom scales (systemic side effects [SE], upset by hair loss, arm symptoms, breast

symptoms). Questions used 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores averaged and transformed to 0-100 scale. High score for functional scale indicated high/better level of functioning/healthy functioning. Negative change from Baseline indicated deterioration in QOL and positive change from Baseline indicated an improvement in QOL. ITT population. "Number of subjects analysed"=participants evaluable for this endpoint. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; EOT (28 days after the last dose, up to Week 56); FU Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2313	2318		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=2313, 2317):Body Image	79.7 (± 23.5)	78.9 (± 23.7)		
Change at Week 13 (n=2048, 2086): Body Image	-12.9 (± 24.7)	-13.9 (± 25.2)		
Change at Week 25 (n=2020, 2050): Body Image	-7.6 (± 23.8)	-7.3 (± 23.4)		
Change at EOT (n=2237, 2261):Body Image	-4.9 (± 23.7)	-6.0 (± 24.6)		
Change at FU Month 18 (n=1887, 1889):Body Image	-0.1 (± 23.3)	-1.3 (± 23.3)		
Change at FU Month 24 (n=1839, 1852):Body Image	0.5 (± 23.6)	0.1 (± 23.5)		
Change at FU Month 36 (n=1789, 1758):Body Image	1.7 (± 24.4)	0.7 (± 24.6)		
Baseline (n=966, 997):Sexual Enjoyment	54.0 (± 30.8)	55.0 (± 30.7)		
Change at Week 13 (n=530, 553): Sexual Enjoyment	-16.5 (± 28.4)	-13.1 (± 27.2)		
Change at Week 25 (n=558, 630): Sexual Enjoyment	-11.9 (± 26.8)	-7.9 (± 26.5)		
Change at EOT (n=781, 820):Sexual Enjoyment	-10.7 (± 27.5)	-8.0 (± 27.7)		
Change at FU Month 18(n=585, 581):Sexual Enjoyment	-4.2 (± 28.5)	-6.7 (± 26.5)		
Change at FU Month 24(n=576, 561):Sexual Enjoyment	-6.0 (± 28.4)	-5.0 (± 27.6)		
Change at FU Month 36(n=530, 541):Sexual Enjoyment	-5.3 (± 28.1)	-6.0 (± 26.8)		
Baseline (n=2258, 2260):Sexual Function	19.6 (± 23.8)	20.8 (± 24.3)		
Change at Week 13 (n=1969, 2008): Sexual Function	-5.6 (± 20.5)	-6.6 (± 20.7)		
Change at Week 25 (n=1945, 1975): Sexual Function	-2.6 (± 20.8)	-2.3 (± 20.9)		
Change at EOT (n=2176,2191):Sexual Function	-1.0 (± 20.8)	-1.4 (± 21.2)		
Change at FU Month 18(n=1814,1820):Sexual Function	2.5 (± 22.8)	1.4 (± 21.7)		
Change at FU Month 24(n=1757,1778):Sexual Function	2.8 (± 22.9)	1.8 (± 22.7)		

Change at FU Month 36(n=1711,1685):Sexual Function	2.6 (± 24.0)	1.6 (± 23.6)		
Baseline (n=2312, 2318):FP	51.3 (± 31.7)	50.5 (± 31.5)		
Change at Week 13 (n=2043, 2090): FP	3.1 (± 30.2)	1.8 (± 31.9)		
Change at Week 25 (n=2020, 2052): FP	6.3 (± 31.1)	5.4 (± 31.2)		
Change at EOT (n=2238, 2263): FP	7.7 (± 32.2)	6.9 (± 31.8)		
Change at FU Month 18 (n=1887, 1884):FP	12.9 (± 32.2)	10.5 (± 32.0)		
Change at FU Month 24 (n=1836, 1849):FP	13.7 (± 32.9)	12.9 (± 32.9)		
Change at FU Month 36 (n=1785, 1752):FP	14.7 (± 34.1)	13.6 (± 32.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EORTC QLQ-BR23 Symptom Scale Score

End point title	Change From Baseline in EORTC QLQ-BR23 Symptom Scale Score

End point description:

EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of four functional scales (body image, sexual enjoyment, sexual functioning, future perspective [FP]) and four symptom scales (systemic side effects [SE], upset by hair loss, arm symptoms, breast symptoms). Questions used 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores averaged and transformed to 0-100 scale. High score for symptom scale indicated high level of symptomatology/problems/greater degree of symptoms. Negative change from Baseline indicated deterioration in QOL and positive change from Baseline indicated an improvement in QOL. ITT population. "Number of subjects analysed"=participants evaluable for this endpoint. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; EOT (28 days after the last dose, up to Week 56); FU Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2331	2335		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n=2331, 2335):Systemic SE	9.5 (± 10.9)	10.2 (± 11.2)		
Change at Week 13 (n=2071, 2107): Systemic SE	21.1 (± 17.5)	21.7 (± 17.9)		
Change at Week 25 (n=2043, 2072): Systemic SE	9.2 (± 14.2)	8.2 (± 14.2)		
Change at EOT (n=2258, 2280)	8.3 (± 15.4)	7.5 (± 14.8)		
Change at FU Month 18 (n=1909, 1912):Systemic SE	4.4 (± 12.8)	5.5 (± 13.4)		
Change at FU Month 24 (n=1860, 1871):Systemic SE	4.1 (± 13.2)	4.9 (± 13.7)		

Change at FU Month 36 (n=1812, 1783):Systemic SE	4.5 (± 13.6)	5.2 (± 13.8)		
Baseline (n=356, 340): Hair Loss	26.4 (± 32.8)	22.1 (± 29.0)		
Change at Week 13 (n=208, 206): Hair Loss	17.3 (± 43.6)	21.2 (± 37.8)		
Change at Week 25 (n=100, 101): Hair Loss	8.3 (± 38.0)	14.5 (± 38.4)		
Change at EOT (n=297, 290): Hair Loss	10.9 (± 40.1)	17.9 (± 39.8)		
Change at FU Month 18 (n=71, 104): Hair Loss	-7.0 (± 36.0)	3.2 (± 34.9)		
Change at FU Month 24 (n=73, 92): Hair Loss	-4.1 (± 39.3)	0.7 (± 36.0)		
Change at FU Month 36 (n=95, 111): Hair Loss	-5.6 (± 42.3)	2.4 (± 34.7)		
Baseline (n=2326, 2331): Arm Symptoms	21.6 (± 19.1)	21.7 (± 19.2)		
Change at Week 13 (n=2064, 2102): Arm Symptoms	-4.7 (± 20.8)	-2.1 (± 21.5)		
Change at Week 25 (n=2037, 2070): Arm Symptoms	-2.9 (± 21.3)	-2.3 (± 21.7)		
Change at EOT (n=2251,2275):Arm Symptoms	-3.5 (± 21.5)	-3.4 (± 21.4)		
Change at FU Month 18 (n=1903, 1913):Arm Symptoms	-4.0 (± 21.8)	-3.9 (± 22.5)		
Change at FU Month 24 (n=1857, 1866):Arm Symptoms	-5.1 (± 21.6)	-5.0 (± 22.3)		
Change at FU Month 36 (n=1809, 1777):Arm Symptoms	-5.9 (± 21.8)	-4.7 (± 22.4)		
Baseline (n=2325, 2330): Breast Symptoms	19.5 (± 17.5)	20.4 (± 17.7)		
Change at Week 13 (n=2063, 2102): Breast Symptoms	-5.0 (± 18.4)	-5.2 (± 18.0)		
Change at Week 25 (n=2036, 2069): Breast Symptoms	1.9 (± 20.7)	-0.4 (± 20.6)		
Change at EOT (n=2250,2275):Breast Symptoms	-0.6 (± 20.2)	-3.8 (± 19.7)		
Change at FU Month 18(n=1903,1911):Breast Symptoms	-3.0 (± 18.7)	-5.9 (± 18.8)		
Change at FU Month 24(n=1857,1865):Breast Symptoms	-6.4 (± 18.4)	-7.3 (± 18.7)		
Change at FU Month 36(n=1808,1775):Breast Symptoms	-7.3 (± 18.8)	-7.9 (± 19.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Response for European Quality of Life-5 Dimensions-3 Level (EQ-5D-3L) Questionnaire: Mobility Domain

End point title	Percentage of Participants With Response for European Quality of Life-5 Dimensions-3 Level (EQ-5D-3L) Questionnaire: Mobility Domain

End point description:

EQ-5D-3L is a descriptive system of health-related quality of life states consisting of 5 dimensions/domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each of which has 3 levels of severity (no problems [scored as 1], some or moderate problems [scored as 2], and extreme problems [scored as 3]). Percentage of participants with each of the following responses in mobility domain was reported: I have no problems in walking about; I have some problems

in walking about; and I am confined to bed. Response percentages may not add up to 100% due to data rounding. ITT population. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; EOT (28 days after the last dose, up to Week 56); FU Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)				
Baseline (n=2292, 2310): No problems	93.8	92.9		
Baseline (n=2292, 2310): Some problems	6.2	6.9		
Baseline (n=2292, 2310): Confined to bed	0.0	0.2		
Week 13 (n=2080, 2129): No problems	77.5	74.8		
Week 13 (n=2080, 2129): Some problems	22.1	24.8		
Week 13 (n=2080, 2129): Confined to bed	0.4	0.4		
Week 25 (n=2062, 2081): No problems	83.8	82.7		
Week 25 (n=2062, 2081): Some problems	16.1	17.2		
Week 25 (n=2062, 2081): Confined to bed	0.1	0.1		
EOT (n=2051, 2106): No problems	85.1	84.9		
EOT (n=2051, 2106): Some problems	14.8	14.9		
EOT (n=2051, 2106): Confined to bed	0.1	0.2		
FU Month 18 (n=1920, 1919): No problems	88.8	87.0		
FU Month 18 (n=1920, 1919): Some problems	11.2	12.8		
FU Month 18 (n=1920, 1919): Confined to bed	0.1	0.2		
FU Month 24 (n=1864, 1877): No problems	87.8	87.7		
FU Month 24 (n=1864, 1877): Some problems	12.1	12.1		
FU Month 24 (n=1864, 1877): Confined to bed	0.1	0.1		
FU Month 36 (n=1822, 1795): No problems	88.5	87.8		
FU Month 36 (n=1822, 1795): Some problems	11.5	12.1		
FU Month 36 (n=1822, 1795): Confined to bed	0.0	0.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Response for EQ-5D-3L Questionnaire: Self-Care Domain

End point title	Percentage of Participants With Response for EQ-5D-3L Questionnaire: Self-Care Domain

End point description:

EQ-5D-3L is a descriptive system of health-related quality of life states consisting of 5 dimensions/domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each of which has 3 levels of severity (no problems [scored as 1], some or moderate problems [scored as 2], and extreme problems [scored as 3]). Percentage of participants with each of the following responses in self-care domain was reported: I have no problems with self-care; I have some problems washing or dressing myself; and I am unable to wash or dress myself. Response percentages may not add up to 100% due to data rounding. ITT population. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; EOT (28 days after the last dose, up to Week 56); FU Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)				
Baseline (n=2289, 2310): No problems	89.7	90.7		
Baseline (n=2289, 2310): Some problems	10.0	9.1		
Baseline (n=2289, 2310): Unable	0.3	0.2		
Week 13 (n=2079, 2127): No problems	94.3	93.2		
Week 13 (n=2079, 2127): Some problems	5.3	6.4		
Week 13 (n=2079, 2127): Unable	0.4	0.4		
Week 25 (n=2057, 2077): No problems	95.5	95.0		
Week 25 (n=2057, 2077): Some problems	4.3	4.7		
Week 25 (n=2057, 2077): Unable	0.1	0.3		
EOT (n=2051, 2106): No problems	95.4	95.8		
EOT (n=2051, 2106): Some problems	4.4	4.0		
EOT (n=2051, 2106): Unable	0.2	0.2		
FU Month 18 (n=1917, 1921): No problems	97.2	96.0		
FU Month 18 (n=1917, 1921): Some problems	2.6	3.6		
FU Month 18 (n=1917, 1921): Unable	0.2	0.3		
FU Month 24 (n=1861, 1877): No problems	96.9	96.3		
FU Month 24 (n=1861, 1877): Some problems	2.8	3.5		
FU Month 24 (n=1861, 1877): Unable	0.3	0.3		
FU Month 36 (n=1822, 1794): No problems	97.3	96.5		

FU Month 36 (n=1822, 1794): Some problems	2.5	3.2		
FU Month 36 (n=1822, 1794): Unable	0.2	0.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Response for EQ-5D-3L Questionnaire: Usual Activities Domain

End point title	Percentage of Participants With Response for EQ-5D-3L Questionnaire: Usual Activities Domain

End point description:

EQ-5D-3L is a descriptive system of health-related quality of life states consisting of 5 dimensions/domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each of which has 3 levels of severity (no problems [scored as 1], some or moderate problems [scored as 2], and extreme problems [scored as 3]). Percentage of participants with each of the following responses in usual activities domain was reported: I have no problems with performing my usual activities; I have some problems with performing my usual activities; and I am unable to perform my usual activities. Response percentages may not add up to 100% due to data rounding. ITT population. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; EOT (28 days after the last dose, up to Week 56); FU Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)				
Baseline (n=2288, 2308): No problems	67.4	66.1		
Baseline (n=2288, 2308): Some problems	30.4	32.2		
Baseline (n=2288, 2308): Unable	2.2	1.7		
Week 13 (n=2078, 2128): No problems	56.8	54.1		
Week 13 (n=2078, 2128): Some problems	40.1	43.0		
Week 13 (n=2078, 2128): Unable	3.1	2.9		
Week 25 (n=2059, 2077): No problems	66.5	65.8		
Week 25 (n=2059, 2077): Some problems	32.2	32.7		
Week 25 (n=2059, 2077): Unable	1.2	1.4		
EOT (n=2049, 2102): No problems	72.4	72.5		
EOT (n=2049, 2102): Some problems	26.3	26.6		
EOT (n=2049, 2102): Unable	1.3	0.9		
FU Month 18 (n=1919, 1918): No problems	78.5	76.3		
FU Month 18 (n=1919, 1918): Some problems	20.6	23.0		

FU Month 18 (n=1919, 1918): Unable	0.9	0.7		
FU Month 24 (n=1862, 1875): No problems	78.7	79.1		
FU Month 24 (n=1862, 1875): Some problems	20.4	19.7		
FU Month 24 (n=1862, 1875): Unable	0.9	1.1		
FU Month 36 (n=1821, 1794): No problems	80.9	79.8		
FU Month 36 (n=1821, 1794): Some problems	18.3	19.4		
FU Month 36 (n=1821, 1794): Unable	0.7	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Response for EQ-5D-3L Questionnaire: Pain/Discomfort Domain

End point title	Percentage of Participants With Response for EQ-5D-3L Questionnaire: Pain/Discomfort Domain

End point description:

EQ-5D-3L is a descriptive system of health-related quality of life states consisting of 5 dimensions/domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each of which has 3 levels of severity (no problems [scored as 1], some or moderate problems [scored as 2], and extreme problems [scored as 3]). Percentage of participants with each of the following responses in pain/discomfort domain was reported: I have no pain or discomfort; I have moderate pain or discomfort; and I have extreme pain or discomfort. Response percentages may not add up to 100% due to data rounding. ITT population. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; EOT (28 days after the last dose, up to Week 56); FU Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)				
Baseline (n=2290, 2310): No pain/discomfort	49.0	49.0		
Baseline (n=2290, 2310): Moderate pain/discomfort	50.0	49.7		
Baseline (n=2290, 2310): Extreme pain/discomfort	1.0	1.3		
Week 13 (n=2076, 2127): No pain/discomfort	44.6	40.5		
Week 13 (n=2076, 2127): Moderate pain/discomfort	52.7	56.5		
Week 13 (n=2076, 2127): Extreme pain/discomfort	2.7	3.0		

Week 25 (n=2062, 2080): No pain/discomfort	44.3	43.7		
Week 25 (n=2062, 2080): Moderate pain/discomfort	53.3	54.4		
Week 25 (n=2062, 2080): Extreme pain/discomfort	2.4	1.9		
EOT (n=2049, 2106): No pain/discomfort	49.3	50.0		
EOT (n=2049, 2106): Moderate pain/discomfort	48.5	47.6		
EOT (n=2049, 2106): Extreme pain/discomfort	2.2	2.4		
FU Month 18 (n=1918, 1918): No pain/discomfort	51.3	53.1		
FU Month 18(n=1918, 1918):Moderate pain/discomfort	46.6	44.7		
FU Month 18(n=1918, 1918):Extreme pain/discomfort	2.1	2.1		
FU Month 24 (n=1863, 1879): No pain/discomfort	56.7	56.0		
FU Month 24(n=1863, 1879):Moderate pain/discomfort	41.3	41.5		
FU Month 24(n=1863, 1879):Extreme pain/discomfort	1.9	2.5		
FU Month 36 (n=1823, 1793): No pain/discomfort	59.5	57.8		
FU Month 36(n=1823, 1793):Moderate pain/discomfort	38.9	40.1		
FU Month 36(n=1823, 1793):Extreme pain/discomfort	1.6	2.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Response for EQ-5D-3L Questionnaire: Anxiety/Depression Domain

End point title	Percentage of Participants With Response for EQ-5D-3L Questionnaire: Anxiety/Depression Domain

End point description:

EQ-5D-3L is a descriptive system of health-related quality of life states consisting of 5 dimensions/domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each of which has 3 levels of severity (no problems [scored as 1], some or moderate problems [scored as 2], and extreme problems [scored as 3]). Percentage of participants with each of the following responses in anxiety/depression domain was reported: I am not anxious or depressed; I am moderately anxious or depressed; and I am extremely anxious or depressed. Response percentages may not add up to 100% due to data rounding. ITT population. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 13, 25; EOT (28 days after the last dose, up to Week 56); FU Months 18, 24, 36

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: percentage of participants				
number (not applicable)				
Baseline (n=2286, 2310): Not anxious/depress	47.1	44.7		
Baseline (n=2286, 2310): Moderate anxious/depress	49.4	50.1		
Baseline (n=2286, 2310): Extreme anxious/depress	3.5	5.2		
Week 13 (n=2076, 2125): Not anxious/depress	53.6	52.4		
Week 13 (n=2076, 2125): Moderate anxious/depress	43.4	44.0		
Week 13 (n=2076, 2125): Extreme anxious/depress	3.0	3.7		
Week 25 (n=2060, 2075): Not anxious/depress	55.5	55.5		
Week 25 (n=2060, 2075): Moderate anxious/depress	41.9	41.8		
Week 25 (n=2060, 2075): Extreme anxious/depress	2.5	2.7		
EOT (n=2041,2101):Not anxious/depress	58.5	58.3		
EOT (n=2041, 2101): Moderate anxious/depress	38.9	39.1		
EOT (n=2041, 2101): Extreme anxious/depress	2.6	2.6		
FU Month 18(n=1916,1915):Not anxious/depress	61.4	59.9		
FU Month 18(n=1916,1915):Moderate anxious/depress	36.2	37.0		
FU Month 18(n=1916,1915):Extreme anxious/depress	2.4	3.1		
FU Month 24(n=1860,1872):Not anxious/depress	63.8	61.0		
FU Month 24(n=1860,1872):Moderate anxious/depress	33.8	36.2		
FU Month 24(n=1860,1872):Extreme anxious/depress	2.4	2.8		
FU Month 36(n=1815,1787):Not anxious/depress	64.0	61.6		
FU Month 36(n=1815,1787):Moderate anxious/depress	33.3	35.4		
FU Month 36(n=1815,1787):Extreme anxious/depress	2.6	3.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Serum Concentration (Cmin) of Pertuzumab

End point title	Trough Serum Concentration (Cmin) of Pertuzumab

End point description:

Pharmacokinetic (PK) evaluable participants were defined as those who received at least one active pertuzumab and/or trastuzumab treatment and had at least one PK sample collected. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Cycles 1, 10 and 15 (Cycle length=21 days)

End point values	Pertuzumab + Trastuzumab + Chemotherapy			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Cycle 1 (n=31)	68.0 (± 16.6)			
Cycle 10 (n=31)	88.1 (± 34.4)			
Cycle 15 (n=27)	95.5 (± 51.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin of Trastuzumab

End point title	Cmin of Trastuzumab

End point description:

PK evaluable participants. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Cycles 1, 10 and 15 (Cycle length=21 days)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	34		
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1 (n=32, 31)	32.1 (± 13.4)	34.1 (± 11.4)		
Cycle 10 (n=33, 26)	65.0 (± 39.6)	68.4 (± 23.0)		
Cycle 15 (n=27, 22)	72.9 (± 46.1)	71.0 (± 30.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Peak Serum Concentration (Cmax) of Pertuzumab

End point title	Peak Serum Concentration (Cmax) of Pertuzumab

End point description:

PK evaluable participants. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Cycles 1, 10 and 15 (Cycle length=21 days)

End point values	Pertuzumab + Trastuzumab + Chemotherapy			
Subject group type	Subject analysis set			
Number of subjects analysed	36			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1 (n=33)	237 (± 118)			
Cycle 10 (n=29)	222 (± 92.2)			
Cycle 15 (n=24)	206 (± 94.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Trastuzumab

End point title	Cmax of Trastuzumab

End point description:

PK evaluable participants. Here, n=participants evaluable for this endpoint at specified timepoint.

End point type	Secondary

End point timeframe:

Cycles 1, 10 and 15 (Cycle length=21 days)

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	34		
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1 (n=36, 33)	180 (± 81.0)	190 (± 51.6)		
Cycle 10 (n=33, 27)	219 (± 94.6)	225 (± 70.7)		
Cycle 15 (n=25, 21)	187 (± 95.1)	234 (± 73.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization until data cut-off date 19 December 2016 (up to maximum length of follow-up of 59 months)

Adverse event reporting additional description:

Safety population. 38 participants randomized to pertuzumab arm received study treatment but did not receive pertuzumab and were included in the placebo arm for safety analyses. 24 participants randomized to placebo arm received at least 1 dose of pertuzumab and were included in pertuzumab arm for safety analyses.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Chemotherapy

Reporting group description:

Participants received pertuzumab (840 mg loading dose, then 420 mg) and trastuzumab (8 mg/kg loading dose, then 6 mg/kg) IV Q3W for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m^2 + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin AUC 6 (up to 900 mg).

Reporting group title	Placebo + Trastuzumab + Chemotherapy

Reporting group description:

Participants received placebo matched to pertuzumab IV Q3W and trastuzumab (8 mg/kg loading dose, then 6 mg/kg) IV Q3W for 1 year (maximum 18 cycles) in combination with 1 of the following IV chemotherapy regimen (anthracycline-based or nonanthracycline-based) per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m^2 + epirubicin 90-120 mg/m^2 or doxorubicin 50 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W (100 mg/m^2 for 3 cycles, 75 mg/m^2 in first cycle and 100 mg/m^2 in subsequent cycles, or 75 mg/m^2 for 4 cycles) or 12 cycles of paclitaxel 80 mg/m^2 QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m^2 or epirubicin 90-120 mg/m^2 + cyclophosphamide 500-600 mg/m^2 followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (as described in Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m^2 + carboplatin AUC 6 (up to 900 mg).

Serious adverse events	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	692 / 2364 (29.27%)	585 / 2405 (24.32%)	
number of deaths (all causes)	73	95	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			

subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Basal cell carcinoma			
subjects affected / exposed	1 / 2364 (0.04%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign breast neoplasm			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric neoplasm			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric cancer			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lentigo maligna			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoclonal gammopathy			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurilemmoma benign			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer metastatic			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parathyroid tumour benign			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic neoplasm			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma			
subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Axillary vein thrombosis			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 2364 (0.08%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	3 / 2364 (0.13%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	2 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 2364 (0.04%)	4 / 2405 (0.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 2364 (0.08%)	5 / 2405 (0.21%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			

subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 2364 (0.04%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 2364 (0.00%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 2364 (0.08%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	4 / 2364 (0.17%)	6 / 2405 (0.25%)	
occurrences causally related to treatment / all	0 / 4	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related thrombosis			
subjects affected / exposed	1 / 2364 (0.04%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	7 / 2364 (0.30%)	5 / 2405 (0.21%)	
occurrences causally related to treatment / all	5 / 10	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	5 / 2364 (0.21%)	5 / 2405 (0.21%)	
occurrences causally related to treatment / all	2 / 5	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	2 / 2364 (0.08%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	3 / 2364 (0.13%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mass			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	4 / 2364 (0.17%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	39 / 2364 (1.65%)	45 / 2405 (1.87%)	
occurrences causally related to treatment / all	11 / 40	9 / 52	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 2364 (0.04%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	3 / 2364 (0.13%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	11 / 2364 (0.47%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	6 / 11	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast inflammation			
subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast pain			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical polyp			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Menorrhagia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic cyst			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 2364 (0.04%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchospasm			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	2 / 2364 (0.08%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 2364 (0.25%)	7 / 2405 (0.29%)	
occurrences causally related to treatment / all	2 / 6	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	3 / 2364 (0.13%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 2364 (0.04%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung consolidation			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal oedema			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal discomfort			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 2364 (0.08%)	4 / 2405 (0.17%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 2364 (0.04%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 2364 (0.21%)	5 / 2405 (0.21%)	
occurrences causally related to treatment / all	1 / 5	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary fibrosis			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusional disorder, unspecified type			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	5 / 2364 (0.21%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	1 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomania			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persistent depressive disorder			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychogenic seizure			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reactive psychosis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	3 / 2364 (0.13%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Product issues			
Device breakage			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device extrusion			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 2364 (0.04%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	11 / 2364 (0.47%)	7 / 2405 (0.29%)	
occurrences causally related to treatment / all	11 / 12	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	7 / 2364 (0.30%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	3 / 8	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose fluctuation			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			

subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Avulsion fracture			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft thrombosis			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus facture			
subjects affected / exposed	5 / 2364 (0.21%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	3 / 2364 (0.13%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoconiosis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary radiation injury			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation skin injury			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	3 / 2364 (0.13%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seroma			
subjects affected / exposed	0 / 2364 (0.00%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	3 / 2364 (0.13%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			

subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	2 / 2364 (0.08%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Aplasia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyloric stenosis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 2364 (0.13%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	3 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	33 / 2364 (1.40%)	17 / 2405 (0.71%)	
occurrences causally related to treatment / all	32 / 35	16 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrasystoles			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic cardiomyopathy			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	4 / 2364 (0.17%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 2364 (0.08%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia paroxysmal			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 2364 (0.04%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	2 / 2364 (0.08%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic nervous system imbalance			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	3 / 2364 (0.13%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial neuralgia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head titubation			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with aura			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurotoxicity			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	3 / 2364 (0.13%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sunct syndrome			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	13 / 2364 (0.55%)	5 / 2405 (0.21%)	
occurrences causally related to treatment / all	2 / 13	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual field defect			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	10 / 2364 (0.42%)	8 / 2405 (0.33%)	
occurrences causally related to treatment / all	7 / 13	5 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	2 / 2364 (0.08%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytopenia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	9 / 2364 (0.38%)	7 / 2405 (0.29%)	
occurrences causally related to treatment / all	3 / 9	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	208 / 2364 (8.80%)	196 / 2405 (8.15%)	
occurrences causally related to treatment / all	27 / 233	18 / 215	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 2364 (0.13%)	5 / 2405 (0.21%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			

subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic haemolytic anaemia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	26 / 2364 (1.10%)	32 / 2405 (1.33%)	
occurrences causally related to treatment / all	3 / 31	3 / 37	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 2364 (0.08%)	4 / 2405 (0.17%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
External ear inflammation			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden hearing loss			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tympanic membrane perforation			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			

subjects affected / exposed	5 / 2364 (0.21%)	4 / 2405 (0.17%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic nerve disorder			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 2364 (0.25%)	7 / 2405 (0.29%)	
occurrences causally related to treatment / all	0 / 6	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	4 / 2364 (0.17%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 2364 (0.08%)	5 / 2405 (0.21%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Constipation			

subjects affected / exposed	4 / 2364 (0.17%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	58 / 2364 (2.45%)	18 / 2405 (0.75%)	
occurrences causally related to treatment / all	26 / 65	8 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia strangulated			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	2 / 2364 (0.08%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal obstruction			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	18 / 2364 (0.76%)	14 / 2405 (0.58%)	
occurrences causally related to treatment / all	2 / 18	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema mouth			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal pain			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 2364 (0.04%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	4 / 2364 (0.17%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	7 / 2364 (0.30%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	3 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toothache			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 2364 (0.04%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	19 / 2364 (0.80%)	15 / 2405 (0.62%)	
occurrences causally related to treatment / all	1 / 20	2 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis acneiform			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	5 / 2364 (0.21%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 2364 (0.21%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid disorder			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	2 / 2364 (0.08%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 2364 (0.08%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sjogren's syndrome			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess oral			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatitis B			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 2364 (0.04%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis Perforated			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	3 / 2364 (0.13%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	7 / 2364 (0.30%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	14 / 2364 (0.59%)	12 / 2405 (0.50%)	
occurrences causally related to treatment / all	2 / 14	2 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	7 / 2364 (0.30%)	9 / 2405 (0.37%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			

subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated tuberculosis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	3 / 2364 (0.13%)	6 / 2405 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	3 / 2364 (0.13%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	8 / 2364 (0.34%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	1 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected seroma			
subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	7 / 2364 (0.30%)	6 / 2405 (0.25%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	4 / 2364 (0.17%)	3 / 2405 (0.12%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	3 / 2364 (0.13%)	4 / 2405 (0.17%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphangitis			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	4 / 2364 (0.17%)	4 / 2405 (0.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	3 / 2364 (0.13%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	10 / 2364 (0.42%)	4 / 2405 (0.17%)	
occurrences causally related to treatment / all	3 / 11	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis infective			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal infection			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	16 / 2364 (0.68%)	23 / 2405 (0.96%)	
occurrences causally related to treatment / all	4 / 16	2 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 2364 (0.08%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophoritis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	7 / 2364 (0.30%)	9 / 2405 (0.37%)	
occurrences causally related to treatment / all	0 / 7	1 / 11	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
subjects affected / exposed	0 / 2364 (0.00%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Serratia infection			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	2 / 2364 (0.08%)	5 / 2405 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	3 / 2364 (0.13%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			

subjects affected / exposed	1 / 2364 (0.04%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	9 / 2364 (0.38%)	8 / 2405 (0.33%)	
occurrences causally related to treatment / all	1 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	8 / 2364 (0.34%)	9 / 2405 (0.37%)	
occurrences causally related to treatment / all	0 / 11	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 2364 (0.08%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	2 / 2364 (0.08%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	5 / 2364 (0.21%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 2364 (0.25%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	5 / 2364 (0.21%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	18 / 2364 (0.76%)	5 / 2405 (0.21%)	
occurrences causally related to treatment / all	4 / 18	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			

subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 2364 (0.04%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 2364 (0.08%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	8 / 2364 (0.34%)	2 / 2405 (0.08%)	
occurrences causally related to treatment / all	1 / 9	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 2364 (0.04%)	0 / 2405 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			

subjects affected / exposed	1 / 2364 (0.04%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 2364 (0.00%)	1 / 2405 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2350 / 2364 (99.41%)	2370 / 2405 (98.54%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	482 / 2364 (20.39%)	509 / 2405 (21.16%)	
occurrences (all)	520	564	
Hypertension			
subjects affected / exposed	91 / 2364 (3.85%)	122 / 2405 (5.07%)	
occurrences (all)	103	130	
Lymphoedema			
subjects affected / exposed	133 / 2364 (5.63%)	160 / 2405 (6.65%)	
occurrences (all)	136	166	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	504 / 2364 (21.32%)	499 / 2405 (20.75%)	
occurrences (all)	930	904	
Fatigue			
subjects affected / exposed	1150 / 2364 (48.65%)	1063 / 2405 (44.20%)	
occurrences (all)	1764	1617	
Influenza like illness			
subjects affected / exposed	125 / 2364 (5.29%)	119 / 2405 (4.95%)	
occurrences (all)	156	148	

Mucosal inflammation			
subjects affected / exposed	549 / 2364 (23.22%)	447 / 2405 (18.59%)	
occurrences (all)	744	586	
Oedema			
subjects affected / exposed	139 / 2364 (5.88%)	156 / 2405 (6.49%)	
occurrences (all)	160	176	
Oedema peripheral			
subjects affected / exposed	405 / 2364 (17.13%)	483 / 2405 (20.08%)	
occurrences (all)	489	580	
Pain			
subjects affected / exposed	157 / 2364 (6.64%)	165 / 2405 (6.86%)	
occurrences (all)	186	200	
Pyrexia			
subjects affected / exposed	446 / 2364 (18.87%)	433 / 2405 (18.00%)	
occurrences (all)	633	607	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	372 / 2364 (15.74%)	349 / 2405 (14.51%)	
occurrences (all)	466	434	
Dyspnoea			
subjects affected / exposed	279 / 2364 (11.80%)	272 / 2405 (11.31%)	
occurrences (all)	327	320	
Epistaxis			
subjects affected / exposed	428 / 2364 (18.10%)	325 / 2405 (13.51%)	
occurrences (all)	513	412	
Oropharyngeal pain			
subjects affected / exposed	215 / 2364 (9.09%)	175 / 2405 (7.28%)	
occurrences (all)	256	202	
Rhinorrhoea			
subjects affected / exposed	191 / 2364 (8.08%)	135 / 2405 (5.61%)	
occurrences (all)	210	150	
Psychiatric disorders			
Anxiety			

subjects affected / exposed	151 / 2364 (6.39%)	109 / 2405 (4.53%)	
occurrences (all)	165	112	
Insomnia			
subjects affected / exposed	404 / 2364 (17.09%)	400 / 2405 (16.63%)	
occurrences (all)	454	454	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	220 / 2364 (9.31%)	242 / 2405 (10.06%)	
occurrences (all)	280	322	
Aspartate aminotransferase increased			
subjects affected / exposed	145 / 2364 (6.13%)	162 / 2405 (6.74%)	
occurrences (all)	176	214	
Ejection fraction decreased			
subjects affected / exposed	115 / 2364 (4.86%)	142 / 2405 (5.90%)	
occurrences (all)	129	154	
Neutrophil count decreased			
subjects affected / exposed	324 / 2364 (13.71%)	329 / 2405 (13.68%)	
occurrences (all)	690	695	
Weight decreased			
subjects affected / exposed	191 / 2364 (8.08%)	76 / 2405 (3.16%)	
occurrences (all)	202	81	
Weight increased			
subjects affected / exposed	59 / 2364 (2.50%)	130 / 2405 (5.41%)	
occurrences (all)	61	140	
White blood cell count decreased			
subjects affected / exposed	233 / 2364 (9.86%)	206 / 2405 (8.57%)	
occurrences (all)	561	476	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	297 / 2364 (12.56%)	266 / 2405 (11.06%)	
occurrences (all)	306	270	
Nervous system disorders			
Dizziness			

subjects affected / exposed	269 / 2364 (11.38%)	274 / 2405 (11.39%)	
occurrences (all)	347	358	
Dysgeusia			
subjects affected / exposed	614 / 2364 (25.97%)	518 / 2405 (21.54%)	
occurrences (all)	736	666	
Headache			
subjects affected / exposed	531 / 2364 (22.46%)	561 / 2405 (23.33%)	
occurrences (all)	786	800	
Neuropathy peripheral			
subjects affected / exposed	365 / 2364 (15.44%)	369 / 2405 (15.34%)	
occurrences (all)	424	417	
Paraesthesia			
subjects affected / exposed	276 / 2364 (11.68%)	239 / 2405 (9.94%)	
occurrences (all)	337	277	
Peripheral sensory neuropathy			
subjects affected / exposed	426 / 2364 (18.02%)	422 / 2405 (17.55%)	
occurrences (all)	503	485	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	648 / 2364 (27.41%)	553 / 2405 (22.99%)	
occurrences (all)	794	688	
Leukopenia			
subjects affected / exposed	214 / 2364 (9.05%)	220 / 2405 (9.15%)	
occurrences (all)	452	476	
Neutropenia			
subjects affected / exposed	574 / 2364 (24.28%)	538 / 2405 (22.37%)	
occurrences (all)	998	944	
Eye disorders			
Dry eye			
subjects affected / exposed	140 / 2364 (5.92%)	112 / 2405 (4.66%)	
occurrences (all)	145	116	
Lacrimation increased			
subjects affected / exposed	310 / 2364 (13.11%)	322 / 2405 (13.39%)	
occurrences (all)	332	344	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	281 / 2364 (11.89%)	255 / 2405 (10.60%)	
occurrences (all)	363	328	
Abdominal pain upper			
subjects affected / exposed	241 / 2364 (10.19%)	217 / 2405 (9.02%)	
occurrences (all)	298	292	
Constipation			
subjects affected / exposed	681 / 2364 (28.81%)	758 / 2405 (31.52%)	
occurrences (all)	1014	1107	
Diarrhoea			
subjects affected / exposed	1657 / 2364 (70.09%)	1078 / 2405 (44.82%)	
occurrences (all)	3346	1772	
Dry mouth			
subjects affected / exposed	148 / 2364 (6.26%)	136 / 2405 (5.65%)	
occurrences (all)	164	172	
Gastrooesophageal reflux disease			
subjects affected / exposed	120 / 2364 (5.08%)	107 / 2405 (4.45%)	
occurrences (all)	140	119	
Haemorrhoids			
subjects affected / exposed	183 / 2364 (7.74%)	124 / 2405 (5.16%)	
occurrences (all)	215	138	
Nausea			
subjects affected / exposed	1628 / 2364 (68.87%)	1571 / 2405 (65.32%)	
occurrences (all)	2926	2875	
Stomatitis			
subjects affected / exposed	665 / 2364 (28.13%)	572 / 2405 (23.78%)	
occurrences (all)	996	827	
Vomiting			
subjects affected / exposed	761 / 2364 (32.19%)	725 / 2405 (30.15%)	
occurrences (all)	1213	1170	
Dyspepsia			
subjects affected / exposed	325 / 2364 (13.75%)	341 / 2405 (14.18%)	
occurrences (all)	376	407	

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1577 / 2364 (66.71%)	1610 / 2405 (66.94%)	
occurrences (all)	1585	1622	
Dry skin			
subjects affected / exposed	311 / 2364 (13.16%)	268 / 2405 (11.14%)	
occurrences (all)	346	291	
Erythema			
subjects affected / exposed	234 / 2364 (9.90%)	214 / 2405 (8.90%)	
occurrences (all)	274	272	
Nail discolouration			
subjects affected / exposed	175 / 2364 (7.40%)	178 / 2405 (7.40%)	
occurrences (all)	183	181	
Nail disorder			
subjects affected / exposed	280 / 2364 (11.84%)	284 / 2405 (11.81%)	
occurrences (all)	299	301	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	216 / 2364 (9.14%)	157 / 2405 (6.53%)	
occurrences (all)	237	168	
Pruritus			
subjects affected / exposed	331 / 2364 (14.00%)	217 / 2405 (9.02%)	
occurrences (all)	399	272	
Rash			
subjects affected / exposed	604 / 2364 (25.55%)	487 / 2405 (20.25%)	
occurrences (all)	782	634	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	678 / 2364 (28.68%)	781 / 2405 (32.47%)	
occurrences (all)	895	1117	
Back pain			
subjects affected / exposed	207 / 2364 (8.76%)	237 / 2405 (9.85%)	
occurrences (all)	248	267	
Bone pain			

subjects affected / exposed	223 / 2364 (9.43%)	256 / 2405 (10.64%)	
occurrences (all)	285	345	
Muscle spasms			
subjects affected / exposed	217 / 2364 (9.18%)	123 / 2405 (5.11%)	
occurrences (all)	269	148	
Musculoskeletal pain			
subjects affected / exposed	201 / 2364 (8.50%)	215 / 2405 (8.94%)	
occurrences (all)	241	256	
Myalgia			
subjects affected / exposed	613 / 2364 (25.93%)	708 / 2405 (29.44%)	
occurrences (all)	823	964	
Pain in extremity			
subjects affected / exposed	234 / 2364 (9.90%)	252 / 2405 (10.48%)	
occurrences (all)	274	311	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	147 / 2364 (6.22%)	124 / 2405 (5.16%)	
occurrences (all)	160	130	
Nasopharyngitis			
subjects affected / exposed	315 / 2364 (13.32%)	284 / 2405 (11.81%)	
occurrences (all)	473	414	
Rhinitis			
subjects affected / exposed	141 / 2364 (5.96%)	116 / 2405 (4.82%)	
occurrences (all)	167	130	
Upper respiratory tract infection			
subjects affected / exposed	184 / 2364 (7.78%)	173 / 2405 (7.19%)	
occurrences (all)	227	222	
Urinary tract infection			
subjects affected / exposed	180 / 2364 (7.61%)	155 / 2405 (6.44%)	
occurrences (all)	228	188	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	561 / 2364 (23.73%)	478 / 2405 (19.88%)	
occurrences (all)	912	737	
Hypokalaemia			

subjects affected / exposed	150 / 2364 (6.35%)	97 / 2405 (4.03%)	
occurrences (all)	192	112	
Hypomagnesaemia			
subjects affected / exposed	145 / 2364 (6.13%)	78 / 2405 (3.24%)	
occurrences (all)	177	94	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2012	This amendment was made mainly to adjust for a higher than expected rate of recruitment of node-negative participants. The trial sample size was increased from N=3806 to N=4800 and node-negative participants were no longer permitted to enroll. The recruitment period was adjusted (from 27 to 25 months) and a clause was included to ensure that the primary analysis did not take place until at least 30 months after the last participant enrolled. Additional protocol revisions included following: - The time from randomization to first treatment was increased from 7 weeks to 8 weeks to allow participants more time to enter study. - The number of centers was reduced from 700 to 600. - The number of cycles of 5 fluorouracil, epirubicin and cyclophosphamide (FEC)/5-fluorouracil, doxorubicin and cyclophosphamide (FAC) was made more flexible (3 or 4) to more closely reflect local practice. - Reporting of non-breast second primary malignancies was added, in line with protocol-specified endpoints. - The minimum observation period after administration of pertuzumab was adjusted to align with the current pertuzumab label. - The order of administration of docetaxel, carboplatin and trastuzumab (TCH) was updated in line with current practice, in addition to clarifying the dose and time period of administration. - A range of clarifications were added including to the eligibility criteria (examples of concurrent serious diseases added), the requirements for participants undergoing sentinel lymph node biopsies, the reporting of concomitant medications and prior treatments for breast cancer, the information to be collected at the time of partial withdrawal from the study, and to the timing of assessments and sample collection.
03 December 2013	This amendment consisted mainly of clarifications, corrections of minor inconsistencies and minor adjustments, as follows: - A 3-day window for the last dose of targeted therapy was added at the end of 52 weeks. - The investigational medicinal product (IMP) terminology was clarified to refer specifically to pertuzumab ('targeted treatment' referred to pertuzumab + trastuzumab; 'study drugs' referred to pertuzumab + trastuzumab + chemotherapy). - Due to multiple queries from sites, the language associated with the investigators' choice of adjuvant chemotherapy was revised, and information on excluded anti-cancer agents was added. - Follow-up of adverse events was clarified (until resolution or end of study); also the assessment schedules for participants according to treatments received. Footnotes to the schedule of assessment tables were also added or revised, for example relating to the requirements for yearly mammograms. - Mentions of optional cores from the original tumor block for non-heritable factors were removed.
02 February 2015	This amendment was made primarily to include details of enhanced measures for reporting of pregnancies that occur during study treatment or within 6 months after completion of pertuzumab treatment. In addition, the following changes were made: - The washout period for trastuzumab was increased to 7 months based on updated half-life data for trastuzumab. - Related warnings (pregnancy exclusion and cardiac toxicity risk) were revised based on the updated trastuzumab washout period. - Endocrine therapy recommendations were revised (to allow endocrine therapy administration as per local practice). - An additional plasma sample at disease recurrence was added. - Various clarifications were made (to sample collection, definitions and reporting requirements).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported