



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	28 November 2024

Results information

Result version number	v2 (current)
This version publication date	26 November 2025
First version publication date	22 December 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BO25126
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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, Ltd.
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4058
Public contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 November 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2016
Global end of trial reached?	Yes
Global end of trial date	28 November 2024
Was the trial ended prematurely?	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	Safety, Efficacy
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: 110
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	Czechia: 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: 49
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	2280

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:

Overall, 4804 patients were randomized in the study, 2400 in the Pertuzumab arm and 2404 in the Placebo arm.

Pre-assignment

Screening details:

A total of 6263 patients were screened for the study. The most common cause of screen failure was lack of confirmation of HER2-positivity by the central laboratory which accounted for approximately half of the screen failures.

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/m² + epirubicin 90-120 mg/m² or doxorubicin 50 mg/m² + cyclophosphamide 500-600 mg/m² followed by either 3-4 cycles of docetaxel Q3W (100 mg/m² for 3 cycles, 75 mg/m² in first cycle and 100 mg/m² in subsequent cycles, or 75 mg/m² for 4 cycles) or 12 cycles of paclitaxel 80 mg/m² once weekly (QW); 2) 4 cycles (Q3W) of doxorubicin 60 mg/m² or epirubicin 90-120 mg/m² + cyclophosphamide 500-600 mg/m² 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/m² + 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® rhuMAB2C4
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab was administered as per the schedule specified in the arm description.

Arm title	Placebo + Trastuzumab + Chemotherapy
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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/m²) + epirubicin 90-120 mg/m² or doxorubicin 50 mg/m² + cyclophosphamide 500-600 mg/m² followed by either 3-4 cycles of docetaxel Q3W (100 mg/m² for 3 cycles, 75 mg/m² in first cycle and 100 mg/m² in subsequent cycles, or 75 mg/m² for 4 cycles) or 12 cycles of paclitaxel 80 mg/m² QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m² or epirubicin 90-120 mg/m² + cyclophosphamide 500-600 mg/m² 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/m² + carboplatin AUC 6 (up to 900 milligrams [mg]).

Arm type	Placebo
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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 was administered as per the schedule specified in the arm description.

Number of subjects in period 1	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy
Started	2400	2404
Received at Least 1 Dose of Pertuzumab	2340	24 ^[1]
Received any Treatment Except Pertuzumab	38 ^[2]	2367
Entered Follow-Up	2369	2381
Completed	1361	1316
Not completed	1039	1088
Adverse event, serious fatal	41	46
Consent withdrawn by subject	475	466
Physician decision	43	32
Recurrence of disease	181	269
Adverse event, non-fatal	39	42
Contralateral breast cancer	42	28
Lost to follow-up	181	176
Reason not specified	37	29

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These 24 participants randomized to the placebo arm received at least 1 dose of pertuzumab in error. They were included in the pertuzumab arm for safety analyses.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: These 38 participants randomized to the pertuzumab arm did not receive any pertuzumab. They were included in the placebo arm for safety analyses.

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			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2085	2111	4196
From 65-84 years	313	292	605
85 years and over	2	1	3
Age Continuous Units: years			
arithmetic mean	51.7	51.4	-
standard deviation	± 10.9	± 10.7	-
Sex: Female, Male Units: Participants			
Female	2397	2396	4793
Male	3	8	11

Race/Ethnicity, Customized			
Units: Subjects			
White	1705	1694	3399
Black	32	41	73
Asian	590	598	1188
Other	66	69	135
Not reported	7	2	9
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	45	42	87
Not Hispanic or Latino	432	386	818
Unknown or Not Reported	1923	1976	3899
Nodal Status			
The disease status of a participant's lymph nodes (positive or negative and number affected) was one of the study's randomization stratification factors. Nodal status may have taken any of the four categories for participants who enrolled under protocol version A, but only the two categories with positive nodes after protocol version B had been implemented.			
Units: Subjects			
0 Positive Nodes and Tumor ≤ 1 cm	90	84	174
0 Positive Nodes and Tumor > 1 cm	807	818	1625
1 to 3 Positive Nodes	907	900	1807
≥ 4 Positive Nodes	596	602	1198
Adjuvant Chemotherapy Regimen			
The type of adjuvant chemotherapy regimen that the investigator chose for each participant's treatment (anthracycline or non-anthracycline containing regimen) was one of the study's randomization stratification factors.			
Units: Subjects			
Anthracycline containing regimen	1865	1877	3742
Non-anthracycline containing regimen	535	527	1062
Hormone Receptor Status			
Central laboratory assessment of the hormone receptor status (estrogen receptor [ER] and progesterone receptor [PgR] positive or negative) of each participant's tumor tissue sample was conducted at screening. The hormone receptor status was one of the study's randomization stratification factors.			
Units: Subjects			
Negative (ER and PgR negative)	864	858	1722
Positive (ER and/or PgR positive)	1536	1546	3082
Protocol Version at Enrollment			
The protocol version at enrollment (Version A or B) was one of the study's randomization stratification factors. The amendment from protocol version A (28-June-2011) to version B (20-Nov-2012) was made mainly to adjust for a higher than expected rate of recruitment of node-negative patients. Therefore, the trial sample size was increased from N=3806 to N=4800 and node-negative patients were no longer permitted to enroll.			
Units: Subjects			
Protocol Version A	1828	1827	3655
Protocol Version B	572	577	1149

End points

End points reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Chemotherapy
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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/m² + epirubicin 90-120 mg/m² or doxorubicin 50 mg/m² + cyclophosphamide 500-600 mg/m² followed by either 3-4 cycles of docetaxel Q3W (100 mg/m² for 3 cycles, 75 mg/m² in first cycle and 100 mg/m² in subsequent cycles, or 75 mg/m² for 4 cycles) or 12 cycles of paclitaxel 80 mg/m² once weekly (QW); 2) 4 cycles (Q3W) of doxorubicin 60 mg/m² or epirubicin 90-120 mg/m² + cyclophosphamide 500-600 mg/m² 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/m² + carboplatin area under the curve (AUC) 6 (up to 900 mg).

Reporting group title	Placebo + Trastuzumab + Chemotherapy
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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/m²) + epirubicin 90-120 mg/m² or doxorubicin 50 mg/m² + cyclophosphamide 500-600 mg/m² followed by either 3-4 cycles of docetaxel Q3W (100 mg/m² for 3 cycles, 75 mg/m² in first cycle and 100 mg/m² in subsequent cycles, or 75 mg/m² for 4 cycles) or 12 cycles of paclitaxel 80 mg/m² QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m² or epirubicin 90-120 mg/m² + cyclophosphamide 500-600 mg/m² 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/m² + carboplatin AUC 6 (up to 900 milligrams [mg]).

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

Safety population (N=2364; 2340 pertuzumab arm + 24 from placebo arm who received any pertuzumab). Subjects 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 (max 18 cycles) in combination with 1 of the following IV chemotherapy regimen per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m² + epirubicin 90-120 mg/m² or doxorubicin 50 mg/m² + cyclophosphamide 500-600 mg/m² followed by either 3-4 cycles of docetaxel Q3W (100 mg/m² for 3 cycles, 75 mg/m² in first cycle and 100 mg/m² in subsequent cycles, or 75 mg/m² for 4 cycles) or 12 cycles of paclitaxel 80 mg/m² once weekly (QW); 2) 4 cycles (Q3W) of doxorubicin 60 mg/m² or epirubicin 90-120 mg/m² + cyclophosphamide 500-600 mg/m² followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (per Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m² + carboplatin (up to 900 mg).

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

Safety population (N=2405; 2367 placebo arm + 38 from pertuzumab arm who did not receive any pertuzumab). Participants received placebo matched to pertuzumab IV Q3W and trastuzumab (8 mg/kg loading dose, then 6 mg/kg) intravenously (IV) every 3 weeks (Q3W) for 1 year (max 18 cycles) in combination with 1 of the following IV chemotherapy regimen per Investigator's choice: 1) 3-4 cycles (Q3W) of 5-fluorouracil 500-600 mg/m² + epirubicin 90-120 mg/m² or doxorubicin 50 mg/m² + cyclophosphamide 500-600 mg/m² followed by either 3-4 cycles of docetaxel Q3W (100 mg/m² for 3 cycles, 75 mg/m² in first cycle and 100 mg/m² in subsequent cycles, or 75 mg/m² for 4 cycles) or 12 cycles of paclitaxel 80 mg/m² once weekly (QW); 2) 4 cycles (Q3W) of doxorubicin 60 mg/m² or epirubicin 90-120 mg/m² + cyclophosphamide 500-600 mg/m² followed by either 3-4 cycles of docetaxel Q3W or 12 cycles of paclitaxel QW (per Option 1); 3) 6 cycles (Q3W) of docetaxel 75 mg/m² + carboplatin (up to 900 mg).

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

End point type	Primary
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End point timeframe:

Randomization to the first occurrence of IDFS event (excluding SPNBC) (until data cut-off date 19 December 2016; median [range] follow-up: 3.8 [0-4.9] years)

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	IDFS (Excluding SPNBC)
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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.

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 3 Years, 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 3 Years, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings ^[2]
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End point description:

Kaplan-Meier estimate of the percentage of participants who were IDFS event-free (excluding SPNBC) at 3 years is reported. IDFS 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. All SPNBCs and in situ carcinomas (including DCIS and LCIS) and non-melanoma skin cancer were excluded as an event.

End point type	Primary
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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: Kaplan-Meier Estimate of the Percentage of Participants Who Were IDFS Event-Free (Excluding SPNBC) at 6, 8, and 10 Years, 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 6, 8, and 10 Years, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings
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End point description:

The Kaplan-Meier estimates of the percentage of participants who were IDFS event-free (excluding SPNBC) at 6, 8, and 10 years are reported. IDFS event was defined as the first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, or contralateral invasive breast cancer. All SPNBCs and in situ carcinomas (including DCIS and LCIS) and non-melanoma skin cancer

were excluded as an event. Participants who had not had an event at the time of data analysis were censored at the date last known to be alive and event-free. The number analyzed (n) is the number of participants remaining at risk for an event at the time of analysis for each timepoint.

End point type	Secondary
End point timeframe:	
6, 8, and 10 years	

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: Estimate of percentage of participants				
number (confidence interval 95%)				
6 Years (n = 1482, 1421)	90.56 (89.35 to 91.77)	87.76 (86.40 to 89.13)		
8 Years (n = 1677, 1651)	88.43 (87.10 to 89.76)	85.76 (84.32 to 87.21)		
10 Years (n = 1646, 1589)	87.17 (85.77 to 88.57)	83.82 (82.29 to 85.36)		

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
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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).

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; median [range] follow-up: 3.8 [0-4.9] years)	

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	IDFS (Including SPNBC)
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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.

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 3 Years, 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 3 Years, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings
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End point description:

Kaplan-Meier estimate of the percentage of participants who were IDFS event-free (including SPNBC) at 3 years is reported. IDFS-SPNBC 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).

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: Kaplan-Meier Estimate of the Percentage of Participants Who Were IDFS Event-Free (Including SPNBC) at 6, 8, and 10 Years, 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 6, 8, and 10 Years, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings
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End point description:

Kaplan-Meier estimates of the percentage of participants who were IDFS event-free (including SPNBC) at 6, 8, and 10 years are reported. IDFS-SPNBC was defined as the first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, or SPNBC (with the exception of non-melanoma skin cancers and in situ carcinoma of any site). Participants who had not had an event at the time of data analysis were censored at the date last known to be alive and event-free. The number analyzed (n) is the number of participants remaining at risk for an event at the time of analysis for each timepoint.

End point type	Secondary
End point timeframe:	6, 8, and 10 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: Estimate of percentage of participants				
number (confidence interval 95%)				
6 Years (n = 1472, 1407)	89.31 (88.03 to 90.59)	86.42 (85.00 to 87.44)		
8 Years (n = 1665, 1624)	87.08 (85.69 to 88.48)	83.82 (82.29 to 85.34)		
10 Years (n = 1625, 1555)	85.23 (83.74 to 86.71)	81.31 (79.69 to 82.93)		

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
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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.

End point type	Secondary
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End point timeframe:

Randomization to the first occurrence of DFS event (until data cut-off date 19 December 2016; median [range] follow-up: 3.8 [0-4.9] years)

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	DFS
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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.

Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
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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 3 Years, 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 3 Years, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings
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End point description:

Kaplan-Meier estimate of the percentage of participants who were DFS event-free at 3 years is reported. DFS 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.

End point type	Secondary
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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: Kaplan-Meier Estimate of the Percentage of Participants Who Were DFS Event-Free at 6, 8, and 10 Years, 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 6, 8, and 10 Years, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings
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End point description:

Kaplan-Meier estimates of the percentage of participants who were DFS event-free at 6, 8, and 10 years are reported. DFS was defined as the first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, death attributable to any cause, contralateral invasive breast cancer, SPNBC, or contralateral or ipsilateral DCIS. Participants who had not had an event at the time of data analysis were censored at the date last known to be alive and event-free. The number analyzed (n) is the number of participants remaining at risk for an event at the time of analysis for each timepoint.

End point type	Secondary
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End point timeframe:

6, 8, and 10 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: Estimate of percentage of participants				
number (confidence interval 95%)				
6 Years (n = 1464, 1394)	88.99 (87.69 to 90.29)	86.03 (84.59 to 87.47)		
8 Years (n = 1662, 1612)	86.92 (85.52 to 88.32)	83.19 (81.64 to 88.74)		
10 Years (n = 1620, 1540)	85.01 (83.52 to 86.50)	80.54 (78.89 to 82.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died, First Interim Overall Survival Analysis

End point title	Percentage of Participants Who Died, First Interim Overall Survival Analysis
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End point description:

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

End point type	Secondary
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End point timeframe:

Randomization until death due to any cause (until data cut-off date 19 December 2016; median [range] follow-up: 3.8 [0-4.9] years)

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	Overall Survival, First Interim Analysis
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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.

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] - The O'Brien-Fleming stopping boundary of the Lan-DeMets alpha-spending function for the first interim OS analysis was $HR < 0.52$; $p < 0.00001$.

Secondary: Percentage of Participants Who Died, Final Overall Survival Analysis

End point title	Percentage of Participants Who Died, Final Overall Survival Analysis
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End point description:

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

End point type	Secondary
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End point timeframe:

Randomization until death due to any cause (median [range] follow-up: 11.3 [0-12.9] years)

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)	8.5	10.3		

Statistical analyses

Statistical analysis title	Overall Survival, Final Analysis
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.	
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	= 0.0441 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1

Notes:

[6] - The p-value threshold according to the alpha-spending function at this final analysis was 0.0496.

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

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were Alive at 3 Years
End point description: The Kaplan-Meier approach was used to estimate the percentage of participants who were alive at 3 years. Participants who were alive (including lost to follow-up) at the time of the analysis were censored at the date when they were last known to be alive.	
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: Kaplan-Meier Estimate of the Percentage of Participants Who Were Alive at 6, 8, and 10 Years

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were Alive at 6, 8, and 10 Years
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End point description:

The Kaplan-Meier approach was used to estimate the percentage of participants who were alive at 6, 8, and 10 years. Participants who were alive (including lost to follow-up) at the time of the analysis were censored at the date when they were last known to be alive. The number analyzed (n) is the number of participants remaining at risk for an event at the time of analysis for each timepoint.

End point type	Secondary
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End point timeframe:

6, 8, and 10 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: Estimate of percentage of participants				
number (confidence interval 95%)				
6 Years (n = 1544, 1522)	94.78 (93.85 to 95.71)	93.93 (92.93 to 94.92)		
8 Years (n = 1827, 1834)	92.74 (91.66 to 93.82)	91.96 (90.83 to 93.09)		
10 Years (n = 1798, 1742)	91.55 (90.38 to 92.71)	89.79 (88.53 to 91.06)		

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
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End point description:

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

End point type	Secondary
End point timeframe:	
Randomization until local, regional or distant breast cancer recurrence (until data cut-off date 19 December 2016; median [range] follow-up: 3.8 [0-4.9] years)	

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	RFI
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.	
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 6, 8, and 10 Years, 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 6, 8, and 10 Years, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings
End point description:	
Kaplan-Meier estimates of the percentage of participants who were RFI event-free at 6, 8, and 10 years are reported. RFI event was defined as local, regional or distant breast cancer recurrence. Participants who had not had a recurrence event at the time of data analysis were censored at the date last known to be alive or at their date of death. The number analyzed (n) is the number of participants remaining at risk for an event at the time of analysis for each timepoint.	
End point type	Secondary

End point timeframe:

6, 8, and 10 years

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: Estimate of percentage of participants				
number (confidence interval 95%)				
6 Years (n = 1491, 1434)	92.49 (91.40 to 93.59)	89.91 (88.66 to 91.16)		
8 Years (n = 1773, 1741)	92.11 (90.99 to 93.23)	88.88 (87.59 to 90.18)		
10 Years (n = 1752, 1655)	91.87 (90.74 to 93.00)	88.10 (86.76 to 89.44)		

Statistical analyses

No statistical analyses for this end point

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

Kaplan-Meier estimate of the percentage of participants who were RFI event-free at 3 years is reported. RFI event was defined as local, regional or distant breast cancer recurrence. Participants who had not had a recurrence event at the time of data analysis were censored at the date last known to be alive or at their date of death.

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

Kaplan-Meier estimate of the percentage of participants who were DRFI event-free at 3 years is reported. DRFI event was defined as distant breast cancer recurrence. Participants who had not had a distant recurrence event at the time of data analysis were censored at the date last known to be alive or at their date of death.

End point type	Secondary
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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: Kaplan-Meier Estimate of the Percentage of Participants Who Were DRFI Event-Free at 6, 8, and 10 Years, 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 6, 8, and 10 Years, as Assessed Using Radiologic, Histologic Examinations or Laboratory Findings
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End point description:

Kaplan-Meier estimates of the percentage of participants who were DRFI event-free at 6, 8, and 10 years are reported. DRFI event was defined as distant breast cancer recurrence. Participants who had not had a distant recurrence event at the time of data analysis were censored at the date last known to be alive or at their date of death. The number analyzed (n) is the number of participants remaining at risk for an event at the time of analysis for each timepoint.

End point type	Secondary
End point timeframe:	
6, 8, and 10 years	

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2400	2404		
Units: Estimate of percentage of participants				
number (confidence interval 95%)				
6 Years (n = 1511, 1473)	93.37 (92.34 to 94.40)	91.57 (90.42 to 92.72)		
8 Years (n = 1785, 1769)	92.94 (91.88 to 94.01)	90.69 (89.49 to 91.89)		
10 Years (n = 1765, 1684)	92.85 (91.78 to 93.92)	90.01 (88.77 to 91.25)		

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
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End point description:

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

End point type	Secondary
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End point timeframe:

Randomization until distant breast cancer recurrence (until data cut-off date 19 December 2016; median [range] follow-up: 3.8 [0-4.9] years)

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	DRFI
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.	
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: 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 the 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/items (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea and vomiting [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, used 7-point scale (1=very poor to 7=excellent). EORTC QLQ-C30 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 and positive values indicated improvement.	
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
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End point description:

EORTC QLQ-C30 is a cancer-specific instrument with 30 questions used to assess the 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/items (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 and positive values indicated improvement.

End point type	Secondary
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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: Physical (n=2338, 2342)	89.6 (± 12.9)	89.1 (± 13.4)		
Change at Week 13: Physical (n=2077, 2115)	-10.7 (± 17.2)	-10.6 (± 17.7)		
Change at Week 25: Physical (n=2052, 2078)	-4.6 (± 14.5)	-4.3 (± 14.5)		
Change at EOT: Physical (n=2262, 2287)	-4.1 (± 14.7)	-3.2 (± 14.9)		
Change at FU Month 18: Physical (n=1918, 1925)	-0.9 (± 13.5)	-0.9 (± 14.5)		
Change at FU Month 24: Physical (n=1867, 1875)	-0.4 (± 13.8)	-0.3 (± 14.5)		
Change at FU Month 36: Physical (n=1820, 1792)	-0.3 (± 14.1)	-0.1 (± 13.9)		
Baseline: Role (n=2334, 2337)	79.8 (± 24.7)	79.4 (± 25.2)		
Change at Week 13: Role (n=2075, 2111)	-8.0 (± 28.6)	-8.5 (± 29.5)		
Change at Week 25: Role (n=2049, 2073)	-0.7 (± 26.4)	0.4 (± 27.8)		

Change at EOT: Role (n=2258, 2281)	0.4 (± 27.8)	2.3 (± 28.1)		
Change at FU Month 18: Role (n=1916, 1921)	6.1 (± 26.5)	5.7 (± 28.9)		
Change at FU Month 24: Role (n=1865, 1872)	7.3 (± 26.8)	6.9 (± 28.2)		
Change at FU Month 36: Role (n=1817, 1790)	7.9 (± 26.4)	7.6 (± 27.9)		
Baseline: Social (n=2332, 2336)	81.9 (± 22.9)	80.6 (± 24.1)		
Change at Week 13: Social (n=2071, 2110)	-8.7 (± 25.8)	-7.8 (± 27.1)		
Change at Week 25: Social (n=2044, 2072)	-2.2 (± 24.5)	-0.7 (± 26.3)		
Change at EOT: Social (n=2258, 2282)	0.0 (± 25.2)	1.2 (± 26.3)		
Change at FU Month 18: Social (n=1910, 1915)	5.0 (± 23.8)	4.8 (± 26.7)		
Change at FU Month 24: Social (n=1864, 1868)	5.5 (± 24.8)	6.5 (± 26.6)		
Change at FU Month 36: Social (n=1812, 1783)	6.6 (± 24.9)	7.1 (± 27.3)		
Baseline: Cognitive (n=2334, 2341)	88.8 (± 16.6)	87.9 (± 17.9)		
Change at Week 13: Cognitive (n=2073, 2115)	-9.1 (± 20.5)	-9.0 (± 21.4)		
Change at Week 25: Cognitive (n=2046, 2076)	-7.6 (± 20.4)	-7.0 (± 20.8)		
Change at EOT: Cognitive (n=2259, 2287)	-7.7 (± 20.6)	-7.2 (± 21.4)		
Change at FU Month 18: Cognitive (n=1911, 1920)	-6.1 (± 19.6)	-5.8 (± 21.2)		
Change at FU Month 24: Cognitive (n=1865, 1870)	-6.2 (± 20.5)	-5.5 (± 21.7)		
Change at FU Month 36: Cognitive (n=1814, 1786)	-5.4 (± 20.6)	-4.9 (± 21.8)		
Baseline: Emotional (n=2332, 2340)	72.8 (± 22.4)	71.3 (± 22.7)		
Change at Week 13: Emotional (n=2071, 2114)	3.3 (± 22.2)	2.9 (± 22.5)		
Change at Week 25: Emotional (n=2044, 2076)	5.1 (± 22.7)	5.9 (± 22.2)		
Change at EOT: Emotional (n=2257, 2286)	5.6 (± 23.2)	6.2 (± 23.4)		
Change at FU Month 18: Emotional (n=1909, 1918)	7.7 (± 23.4)	7.6 (± 23.4)		
Change at FU Month 24: Emotional (n=1864, 1869)	7.8 (± 23.3)	8.5 (± 24.2)		
Change at FU Month 36: Emotional (n=1812, 1785)	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 Financial Difficulties Subscale Scores

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

EORTC QLQ-C30 is a cancer-specific instrument with 30 questions used to assess the 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/items (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 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 and positive values indicated worsening of financial difficulties.

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
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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.

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: Body Image (n=2313, 2317)	79.7 (± 23.5)	78.9 (± 23.7)		
Change at Week 13: Body Image (n=2048, 2086)	-12.9 (± 24.7)	-13.9 (± 25.2)		
Change at Week 25: Body Image (n=2020, 2050)	-7.6 (± 23.8)	-7.3 (± 23.4)		
Change at EOT: Body Image (n=2237, 2261)	-4.9 (± 23.7)	-6.0 (± 24.6)		
Change at FU Month 18: Body Image (n=1887, 1889)	-0.1 (± 23.3)	-1.3 (± 23.3)		
Change at FU Month 24: Body Image (n=1839, 1852)	0.5 (± 23.6)	0.1 (± 23.5)		
Change at FU Month 36: Body Image (n=1789, 1758)	1.7 (± 24.4)	0.7 (± 24.6)		
Baseline: Sexual Enjoyment (n=966, 997)	54.0 (± 30.8)	55.0 (± 30.7)		
Change at Week 13: Sexual Enjoyment (n=530, 553)	-16.5 (± 28.4)	-13.1 (± 27.2)		
Change at Week 25: Sexual Enjoyment (n=558, 630)	-11.9 (± 26.8)	-7.9 (± 26.5)		
Change at EOT: Sexual Enjoyment (n=781, 820)	-10.7 (± 27.5)	-8.0 (± 27.7)		
Change at FU Month 18: Sexual Enjoyment (n=585, 581)	-4.2 (± 28.5)	-6.7 (± 26.5)		
Change at FU Month 24: Sexual Enjoyment (n=576, 561)	-6.0 (± 28.4)	-5.0 (± 27.6)		
Change at FU Month 36: Sexual Enjoyment (n=530, 541)	-5.3 (± 28.1)	-6.0 (± 26.8)		
Baseline: Sexual Function (n=2258, 2260)	19.6 (± 23.8)	20.8 (± 24.3)		
Change at Week 13: Sexual Function (n=1969, 2008)	-5.6 (± 20.5)	-6.6 (± 20.7)		
Change at Week 25: Sexual Function (n=1945, 1975)	-2.6 (± 20.8)	-2.3 (± 20.9)		
Change at EOT: Sexual Function (n=2176, 2191)	-1.0 (± 20.8)	-1.4 (± 21.2)		
Change at FU Month 18: Sexual Function (n=1814, 1820)	2.5 (± 22.8)	1.4 (± 21.7)		
Change at FU Month 24: Sexual Function (n=1757, 1778)	2.8 (± 22.9)	1.8 (± 22.7)		
Change at FU Month 36: Sexual Function (n=1711, 1685)	2.6 (± 24.0)	1.6 (± 23.6)		
Baseline: FP (n=2312, 2318)	51.3 (± 31.7)	50.5 (± 31.5)		
Change at Week 13: FP (n=2043, 2090)	3.1 (± 30.2)	1.8 (± 31.9)		
Change at Week 25: FP (n=2020, 2052)	6.3 (± 31.1)	5.4 (± 31.2)		
Change at EOT: FP (n=2238, 2263)	7.7 (± 32.2)	6.9 (± 31.8)		
Change at FU Month 18: FP (n=1887, 1884)	12.9 (± 32.0)	10.5 (± 32.0)		
Change at FU Month 24 : FP (n=1836, 1849)	13.7 (± 32.9)	12.9 (± 32.9)		
Change at FU Month 36: FP (n=1785, 1752)	14.7 (± 34.1)	13.6 (± 32.9)		

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
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End point description:

EORTC QLQ-C30 is a cancer-specific instrument with 30 questions used to assess the 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/items (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea and vomiting [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 disease/treatment-related symptom scores were linearly transformed on a scale of 0 to 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicated improvement in symptoms and positive values indicated worsening of

End point type	Secondary
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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: Diarrhea (n=2329, 2339)	5.2 (± 14.4)	5.1 (± 13.5)		
Change at Week 13: Diarrhea (n=2067, 2111)	22.3 (± 29.8)	9.2 (± 23.9)		
Change at Week 25: Diarrhea (n=2043, 2075)	13.2 (± 26.5)	3.3 (± 19.8)		
Change at EOT: Diarrhea (n=2257, 2285)	12.2 (± 26.9)	2.9 (± 20.0)		
Change at FU Month 18: Diarrhea (n=1907, 1919)	-0.5 (± 17.7)	0.2 (± 17.5)		
Change at FU Month 24: Diarrhea (n=1861, 1868)	-0.8 (± 17.4)	0.2 (± 18.3)		
Change at FU Month 36: Diarrhea (n=1810, 1784)	-0.8 (± 16.5)	0.3 (± 16.9)		
Baseline: Fatigue (n=2335, 2341)	22.4 (± 19.7)	23.2 (± 20.5)		
Change at Week 13: Fatigue (n=2074, 2116)	16.1 (± 24.3)	16.2 (± 24.4)		
Change at Week 25: Fatigue (n=2050, 2078)	7.8 (± 22.5)	6.6 (± 22.3)		
Change at EOT: Fatigue (n=2259, 2287)	7.1 (± 23.0)	5.2 (± 23.0)		

Change at FU Month 18: Fatigue (n=1914, 1924)	1.1 (± 21.7)	1.2 (± 22.5)		
Change at FU Month 24: Fatigue (n=1864, 1873)	0.4 (± 22.0)	0.4 (± 22.6)		
Change at FU Month 36: Fatigue (n=1817, 1791)	-0.2 (± 21.8)	0.6 (± 22.8)		
Baseline: Dyspnea (n=2331, 2336)	6.8 (± 15.5)	8.0 (± 17.1)		
Change at Week 13: Dyspnea (n=2067, 2112)	12.3 (± 23.8)	14.6 (± 26.4)		
Change at Week 25: Dyspnea (n=2045, 2073)	6.3 (± 19.9)	6.4 (± 22.1)		
Change at EOT: Dyspnea (n=2254, 2283)	6.6 (± 20.5)	6.5 (± 22.5)		
Change at FU Month 18: Dyspnea (n=1911, 1917)	5.9 (± 21.0)	5.0 (± 21.5)		
Change at FU Month 24: Dyspnea (n=1860, 1870)	5.1 (± 20.5)	5.3 (± 22.4)		
Change at FU Month 36: Dyspnea (n=1814, 1783)	5.1 (± 20.5)	5.3 (± 22.3)		
Baseline: Appetite Loss (n=2335, 2340)	8.5 (± 18.2)	9.1 (± 18.7)		
Change at Week 13: Appetite Loss (n=2073, 2114)	13.6 (± 29.2)	7.7 (± 27.9)		
Change at Week 25: Appetite Loss (n=2049, 2078)	5.2 (± 25.1)	0.3 (± 22.4)		
Change at EOT: Appetite Loss (n=2257, 2286)	3.0 (± 24.5)	-0.9 (± 22.6)		
Change at FU Month 18: Appetite Loss (n=1913, 1924)	-3.0 (± 20.1)	-3.1 (± 21.1)		
Change at FU Month 24: Appetite Loss (n=1814, 1783)	-3.2 (± 20.6)	-3.3 (± 21.0)		
Change at FU Month 36: Appetite Loss (n=1817, 1789)	-3.0 (± 20.4)	-2.7 (± 21.2)		
Baseline: Insomnia (n=2333, 2338)	25.3 (± 27.4)	27.3 (± 28.5)		
Change at Week 13: Insomnia (n=2073, 2111)	6.3 (± 30.3)	5.1 (± 32.2)		
Change at Week 25: Insomnia (n=2049, 2073)	4.3 (± 30.6)	2.0 (± 31.8)		
Change at EOT: Insomnia (n=2257, 2282)	3.2 (± 31.0)	0.9 (± 32.8)		
Change at FU Month 18: Insomnia (n=1913, 1917)	-0.1 (± 31.1)	0.4 (± 32.4)		
Change at FU Month 24: Insomnia (n=1863, 1869)	-1.5 (± 31.3)	-1.1 (± 32.9)		
Change at FU Month 36: Insomnia (n=1816, 1786)	-0.3 (± 31.1)	-0.5 (± 33.5)		
Baseline: N/V (n=2338, 2342)	2.7 (± 8.2)	3.1 (± 9.4)		
Change at Week 13: N/V (n=2077, 2118)	5.6 (± 15.7)	3.7 (± 14.5)		
Change at Week 25: N/V (n=2052, 2079)	1.1 (± 11.8)	0.5 (± 12.4)		
Change at EOT: N/V (n=2261, 2288)	1.6 (± 12.7)	0.8 (± 13.2)		
Change at FU Month 18: N/V (n=1918, 1925)	-0.2 (± 10.5)	-0.4 (± 12.1)		
Change at FU Month 24: N/V (n=1865, 1874)	0.0 (± 10.7)	-0.1 (± 11.8)		
Change at FU Month 36: N/V (n=1819, 1792)	0.3 (± 11.0)	0.2 (± 11.7)		
Baseline: Constipation (n=2335, 2339)	8.7 (± 19.1)	10.0 (± 19.8)		
Change at Week 13: Constipation (n=2066, 2113)	1.4 (± 23.5)	4.1 (± 25.6)		

Change at Week 25: Constipation (n=2047, 2075)	-0.7 (± 21.8)	0.2 (± 22.8)		
Change at EOT: Constipation (n=2256,2285)	0.1 (± 22.4)	0.9 (± 23.3)		
Change at FU Month 18: Constipation (n=1912, 1922)	3.0 (± 23.3)	1.5 (± 23.8)		
Change at FU Month 24: Constipation (n=1865, 1872)	2.1 (± 23.1)	0.6 (± 22.9)		
Change at FU Month 36: Constipation (n=1815, 1784)	2.1 (± 22.9)	1.5 (± 22.7)		
Baseline: Pain (n=2337, 2342)	18.8 (± 21.4)	19.6 (± 22.1)		
Change at Week 13: Pain (n=2077, 2118)	2.3 (± 25.4)	5.0 (± 26.1)		
Change at Week 25: Pain (n=2051, 2080)	1.4 (± 24.1)	1.4 (± 24.9)		
Change at EOT: Pain (n=2261, 2288)	0.1 (± 24.7)	0.5 (± 25.8)		
Change at FU Month 18: Pain (n=1918, 1927)	-1.3 (± 23.3)	-0.5 (± 25.8)		
Change at FU Month 24: Pain (n=1868, 1874)	-1.6 (± 24.2)	-2.2 (± 25.6)		
Change at FU Month 36: Pain (n=1818, 1792)	-2.6 (± 24.4)	-2.3 (± 25.0)		

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
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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.

End point type	Secondary
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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: Systemic SE (n=2331, 2335)	9.5 (± 10.9)	10.2 (± 11.2)		
Change at Week 13: Systemic SE (n=2071, 2107)	21.1 (± 17.5)	21.7 (± 17.9)		

Change at Week 25: Systemic SE (n=2043, 2072)	9.2 (± 14.2)	8.2 (± 14.2)		
Change at EOT: Systemic SE (n=2258, 2280)	8.3 (± 15.4)	7.5 (± 14.8)		
Change at FU Month 18: Systemic SE (n=1909, 1912)	4.4 (± 12.8)	5.5 (± 13.4)		
Change at FU Month 24: Systemic SE (n=1860, 1871)	4.1 (± 13.2)	4.9 (± 13.7)		
Change at FU Month 36: Systemic SE (n=1812, 1783)	4.5 (± 13.6)	5.2 (± 13.8)		
Baseline: Hair Loss (n=356, 340)	26.4 (± 32.8)	22.1 (± 29.0)		
Change at Week 13: Hair Loss (n=208, 206)	17.3 (± 43.6)	21.2 (± 37.8)		
Change at Week 25: Hair Loss (n=100, 101)	8.3 (± 38.0)	14.5 (± 38.4)		
Change at EOT: Hair Loss (n=297, 290)	10.9 (± 40.1)	17.9 (± 39.8)		
Change at FU Month 18: Hair Loss (n=71, 104)	-7.0 (± 36.0)	3.2 (± 34.9)		
Change at FU Month 24: Hair Loss (n=73, 92)	-4.1 (± 39.3)	0.7 (± 36.0)		
Change at FU Month 36: Hair Loss (n=95, 111)	-5.6 (± 42.3)	2.4 (± 34.7)		
Baseline: Arm Symptoms (n=2326, 2331)	21.6 (± 19.1)	21.7 (± 19.2)		
Change at Week 13: Arm Symptoms (n=2064, 2102)	-4.7 (± 20.8)	-2.1 (± 21.5)		
Change at Week 25: Arm Symptoms (n=2037, 2070)	-2.9 (± 21.3)	-2.3 (± 21.7)		
Change at EOT: Arm Symptoms (n=2251,2275)	-3.5 (± 21.5)	-3.4 (± 21.4)		
Change at FU Month 18: Arm Symptoms (n=1903, 1913)	-4.0 (± 21.8)	-3.9 (± 22.5)		
Change at FU Month 24: Arm Symptoms (n=1857, 1866)	-5.1 (± 21.6)	-5.0 (± 22.3)		
Change at FU Month 36: Arm Symptoms (n=1809, 1777)	-5.9 (± 21.8)	-4.7 (± 22.4)		
Baseline: Breast Symptoms (n=2325, 2330)	19.5 (± 17.5)	20.4 (± 17.7)		
Change at Week 13: Breast Symptoms (n=2063, 2102)	-5.0 (± 18.4)	-5.2 (± 18.0)		
Change at Week 25: Breast Symptoms (n=2036, 2069)	1.9 (± 20.7)	-0.4 (± 20.6)		
Change at EOT: Breast Symptoms (n=2250,2275)	-0.6 (± 20.2)	-3.8 (± 19.7)		
Change at FU Month 18:Breast Symptoms(n=1903,1911)	-3.0 (± 18.7)	-5.9 (± 18.8)		
Change at FU Month 24:Breast Symptoms(n=1857,1865)	-6.4 (± 18.4)	-7.3 (± 18.7)		
Change at FU Month 36:Breast Symptoms(n=1808,1775)	-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.	
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: No problems (n=2292, 2310)	93.8	92.9		
Baseline: Some problems (n=2292, 2310)	6.2	6.9		
Baseline: Confined to bed (n=2292, 2310)	0.0	0.2		
Week 13: No problems (n=2080, 2129)	77.5	74.8		
Week 13: Some problems (n=2080, 2129)	22.1	24.8		
Week 13: Confined to bed (n=2080, 2129)	0.4	0.4		
Week 25: No problems (n=2062, 2081)	83.8	82.7		
Week 25: Some problems (n=2062, 2081)	16.1	17.2		
Week 25: Confined to bed (n=2062, 2081)	0.1	0.1		
EOT: No problems (n=2051, 2106)	85.1	84.9		
EOT: Some problems (n=2051, 2106)	14.8	14.9		
EOT: Confined to bed (n=2051, 2106)	0.1	0.2		
FU Month 18: No problems (n=1920, 1919)	88.8	87.0		
FU Month 18: Some problems (n=1920, 1919)	11.2	12.8		
FU Month 18: Confined to bed (n=1920, 1919)	0.1	0.2		
FU Month 24: No problems (n=1864, 1877)	87.8	87.7		
FU Month 24: Some problems (n=1864, 1877)	12.1	12.1		
FU Month 24: Confined to bed (n=1864, 1877)	0.1	0.1		
FU Month 36: No problems (n=1822, 1795)	88.5	87.8		
FU Month 36: Some problems (n=1822, 1795)	11.5	12.1		

FU Month 36: Confined to bed (n=1822, 1795)	0.0	0.1		
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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.	
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: No problems (n=2289, 2310)	89.7	90.7		
Baseline: Some problems (n=2289, 2310)	10.0	9.1		
Baseline: Unable (n=2289, 2310)	0.3	0.2		
Week 13: No problems (n=2079, 2127)	94.3	93.2		
Week 13: Some problems (n=2079, 2127)	5.3	6.4		
Week 13: Unable (n=2079, 2127)	0.4	0.4		
Week 25: No problems (n=2057, 2077)	95.5	95.0		
Week 25: Some problems (n=2057, 2077)	4.3	4.7		
Week 25: Unable (n=2057, 2077)	0.1	0.3		
EOT: No problems (n=2051, 2106)	95.4	95.8		
EOT: Some problems (n=2051, 2106)	4.4	4.0		
EOT: Unable (n=2051, 2106)	0.2	0.2		
FU Month 18: No problems (n=1917, 1921)	97.2	96.0		
FU Month 18: Some problems (n=1917, 1921)	2.6	3.6		
FU Month 18: Unable (n=1917, 1921)	0.2	0.3		

FU Month 24: No problems (n=1861, 1877)	96.9	96.3		
FU Month 24: Some problems (n=1861, 1877)	2.8	3.5		
FU Month 24: Unable (n=1861, 1877)	0.3	0.3		
FU Month 36: No problems (n=1822, 1794)	97.3	96.5		
FU Month 36: Some problems (n=1822, 1794)	2.5	3.2		
FU Month 36: Unable (n=1822, 1794)	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
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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.

End point type	Secondary
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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: No problems (n=2288, 2308)	67.4	66.1		
Baseline: Some problems (n=2288, 2308)	30.4	32.2		
Baseline: Unable (n=2288, 2308)	2.2	1.7		
Week 13: No problems (n=2078, 2128)	56.8	54.1		
Week 13: Some problems (n=2078, 2128)	40.1	43.0		
Week 13: Unable (n=2078, 2128)	3.1	2.9		
Week 25: No problems (n=2059, 2077)	66.5	65.8		
Week 25: Some problems (n=2059, 2077)	32.2	32.7		
Week 25: Unable (n=2059, 2077)	1.2	1.4		
EOT: No problems (n=2049, 2102)	72.4	72.5		

EOT: Some problems (n=2049, 2102)	26.3	26.6		
EOT: Unable (n=2049, 2102)	1.3	0.9		
FU Month 18: No problems (n=1919, 1918)	78.5	76.3		
FU Month 18: Some problems (n=1919, 1918)	20.6	23.0		
FU Month 18: Unable (n=1919, 1918)	0.9	0.7		
FU Month 24: No problems (n=1862, 1875)	78.7	79.1		
FU Month 24: Some problems (n=1862, 1875)	20.4	19.7		
FU Month 24: Unable (n=1862, 1875)	0.9	1.1		
FU Month 36: No problems (n=1821, 1794)	80.9	79.8		
FU Month 36: Some problems (n=1821, 1794)	18.3	19.4		
FU Month 36: Unable (n=1821, 1794)	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
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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.

End point type	Secondary
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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: No pain/discomfort (n=2290, 2310)	49.0	49.0		
Baseline: Moderate pain/discomfort (n=2290, 2310)	50.0	49.7		
Baseline: Extreme pain/discomfort (n=2290, 2310)	1.0	1.3		

Week 13: No pain/discomfort (n=2076, 2127)	44.6	40.5		
Week 13: Moderate pain/discomfort (n=2076, 2127)	52.7	56.5		
Week 13: Extreme pain/discomfort (n=2076, 2127)	2.7	3.0		
Week 25: No pain/discomfort (n=2062, 2080)	44.3	43.7		
Week 25: Moderate pain/discomfort (n=2062, 2080)	53.3	54.4		
Week 25: Extreme pain/discomfort (n=2062, 2080)	2.4	1.9		
EOT: No pain/discomfort (n=2049, 2106)	49.3	50.0		
EOT: Moderate pain/discomfort (n=2049, 2106)	48.5	47.6		
EOT: Extreme pain/discomfort (n=2049, 2106)	2.2	2.4		
FU Month 18: No pain/discomfort(n=1918, 1918)	51.3	53.1		
FU Month 18: Moderate pain/discomfort(n=1918, 1918)	46.6	44.7		
FU Month 18: Extreme pain/discomfort(n=1918, 1918)	2.1	2.1		
FU Month 24: No pain/discomfort(n=1863, 1879)	56.7	56.0		
FU Month 24: Moderate pain/discomfort(n=1863, 1879)	41.3	41.5		
FU Month 24: Extreme pain/discomfort(n=1863, 1879)	1.9	2.5		
FU Month 36: No pain/discomfort(n=1823, 1793)	59.5	57.8		
FU Month 36: Moderate pain/discomfort(n=1823, 1793)	38.9	40.1		
FU Month 36: Extreme pain/discomfort(n=1823, 1793)	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
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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.

End point type	Secondary
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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: Not anxious/depress (n=2286, 2310)	47.1	44.7		
Baseline: Moderate anxious/depress (n=2286, 2310)	49.4	50.1		
Baseline: Extreme anxious/depress (n=2286, 2310)	3.5	5.2		
Week 13: Not anxious/depress (n=2076, 2125)	53.6	52.4		
Week 13: Moderate anxious/depress (n=2076, 2125)	43.4	44.0		
Week 13: Extreme anxious/depress (n=2076, 2125)	3.0	3.7		
Week 25: Not anxious/depress (n=2060, 2075)	55.5	55.5		
Week 25: Moderate anxious/depress (n=2060, 2075)	41.9	41.8		
Week 25: Extreme anxious/depress (n=2060, 2075)	2.5	2.7		
EOT: Not anxious/depress (n=2041,2101)	58.5	58.3		
EOT: Moderate anxious/depress (n=2041,2101)	38.9	39.1		
EOT: Extreme anxious/depress (n=2041,2101)	2.6	2.6		
FU Month 18: Not anxious/depress(n=1916,1915)	61.4	59.9		
FU Month 18: Moderate anxious/depress(n=1916,1915)	36.2	37.0		
FU Month 18: Extreme anxious/depress(n=1916,1915)	2.4	3.1		
FU Month 24: Not anxious/depress(n=1860,1872)	63.8	61.0		
FU Month 24: Moderate anxious/depress(n=1860,1872)	33.8	36.2		
FU Month 24: Extreme anxious/depress(n=1860,1872)	2.4	2.8		
FU Month 36: Not anxious/depress(n=1815,1787)	64.0	61.6		
FU Month 36: Moderate anxious/depress(n=1815,1787)	33.3	35.4		
FU Month 36: Extreme anxious/depress(n=1815,1787)	2.6	3.0		

Statistical analyses

Secondary: Percentage of Participants With Primary Cardiac Event, Primary Analysis

End point title	Percentage of Participants With Primary Cardiac Event, Primary Analysis
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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.

End point type	Secondary
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End point timeframe:

Baseline until data cut-off date 19 December 2016 (median [range] follow-up: 3.8 [0.1-4.9] years)

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	Primary Cardiac Events, Primary Analysis
Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4769
Analysis specification	Pre-specified
Analysis type	
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 Primary Cardiac Event, Final Analysis

End point title	Percentage of Participants With Primary Cardiac Event, Final Analysis
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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.

End point type	Secondary
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End point timeframe:

Baseline until the end of follow-up (median [range] follow-up: 11.3 [0.1-12.9] years)

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)	0.9	0.5		
Heart Failure and LVEF Decline	0.8	0.3		
Cardiac Death (Definite or Probable)	0.1	0.2		

Statistical analyses

Statistical analysis title	Primary Cardiac Events, Final Analysis
Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4769
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Treatment Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.9

Secondary: Percentage of Participants With Secondary Cardiac Event, Primary Analysis

End point title	Percentage of Participants With Secondary Cardiac Event, Primary Analysis
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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).

End point type	Secondary
End point timeframe:	
Baseline until data cut-off date 19 December 2016 (median [range] follow-up: 3.8 [0.1-4.9] years)	

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	Secondary Cardiac Event, Primary Analysis
Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4769
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Treatment Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.9

Secondary: Percentage of Participants With Secondary Cardiac Event, Final Analysis

End point title	Percentage of Participants With Secondary Cardiac Event, Final Analysis
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).	
End point type	Secondary
End point timeframe:	
Baseline until the end of follow-up (median [range] follow-up: 11.3 [0.1-12.9] years)	

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)	2.9	3.0		

Statistical analyses

Statistical analysis title	Secondary Cardiac Event, Final Analysis
Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4769
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Treatment Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.9

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

End point title	Change From Baseline in LVEF to Worst Post-Baseline Value, Primary Analysis
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.
End point type	Secondary
End point timeframe:	Baseline until data cut-off date 19 December 2016 (median [range] follow-up: 3.8 [0.1-4.9] years)

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	65.2 (± 5.9)	65.3 (± 6.1)		
Change to Worst Value	-7.5 (± 6.6)	-7.6 (± 6.7)		

Statistical analyses

Statistical analysis title	Max Decrease in LVEF, Primary Analysis
Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4764
Analysis specification	Pre-specified
Analysis type	
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 LVEF to Worst Post-Baseline Value, Final Analysis

End point title	Change From Baseline in LVEF to Worst Post-Baseline Value, Final Analysis
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.	
End point type	Secondary
End point timeframe:	
Baseline until the end of follow-up (median [range] follow-up: 11.3 [0.1-12.9] years)	

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	65.2 (± 5.9)	65.3 (± 6.1)		
Change to Worst Value	-8.6 (± 6.8)	-8.6 (± 7.0)		

Statistical analyses

Statistical analysis title	Max Decrease in LVEF, Final Analysis
Comparison groups	Pertuzumab + Trastuzumab + Chemotherapy v Placebo + Trastuzumab + Chemotherapy
Number of subjects included in analysis	4764
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Treatment Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.4

Secondary: Trough Serum Concentration (Cmin) of Pertuzumab

End point title	Trough Serum Concentration (Cmin) of Pertuzumab ^[7]
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End point description:

End point type	Secondary
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End point timeframe:

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

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This PK endpoint is only applicable to participants in the pertuzumab arm.

End point values	Pertuzumab + Trastuzumab + Chemotherapy			
Subject group type	Reporting group			
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
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End point description:

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	Reporting group	Reporting group		
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 ^[8]
End point description:	

End point type	Secondary
End point timeframe:	
Cycles 1, 10 and 15 (Cycle length=21 days)	

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This PK endpoint is only applicable to participants in the pertuzumab arm.

End point values	Pertuzumab + Trastuzumab + Chemotherapy			
Subject group type	Reporting group			
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
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End point description:

End point type	Secondary
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End point timeframe:

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

End point values	Pertuzumab + Trastuzumab + Chemotherapy	Placebo + Trastuzumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
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:

From first study treatment until end of follow-up (up to 12.9 years)

Adverse event reporting additional description:

Safety population (Pertuzumab arm: N=2364, 2340 + 24 placebo arm receiving any pertuzumab; Placebo arm: N=2405, 2367 + 38 pertuzumab arm not receiving any pertuzumab]). All AEs were collected until 28 days after last dose (up to 80 weeks). In follow-up, AEs reported were study treatment-related SAEs, cardiac AEs, SPNBC and MDS, and pregnancies.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.1
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Reporting groups

Reporting group title	Placebo + Trastuzumab + Chemotherapy
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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/m² + epirubicin 90-120 mg/m² or doxorubicin 50 mg/m² + cyclophosphamide 500-600 mg/m² followed by either 3-4 cycles of docetaxel Q3W (100 mg/m² for 3 cycles, 75 mg/m² in first cycle and 100 mg/m² in subsequent cycles, or 75 mg/m² for 4 cycles) or 12 cycles of paclitaxel 80 mg/m² QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m² or epirubicin 90-120 mg/m² + cyclophosphamide 500-600 mg/m² 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/m² + carboplatin AUC 6 (up to 900 mg).

Reporting group title	Pertuzumab + Trastuzumab + Chemotherapy
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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/m² + epirubicin 90-120 mg/m² or doxorubicin 50 mg/m² + cyclophosphamide 500-600 mg/m² followed by either 3-4 cycles of docetaxel Q3W (100 mg/m² for 3 cycles, 75 mg/m² in first cycle and 100 mg/m² in subsequent cycles, or 75 mg/m² for 4 cycles) or 12 cycles of paclitaxel 80 mg/m² QW; 2) 4 cycles (Q3W) of doxorubicin 60 mg/m² or epirubicin 90-120 mg/m² + cyclophosphamide 500-600 mg/m² 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/m² + carboplatin area under the curve (AUC) 6 (up to 900 mg).

Serious adverse events	Placebo + Trastuzumab + Chemotherapy	Pertuzumab + Trastuzumab + Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	686 / 2405 (28.52%)	792 / 2364 (33.50%)	
number of deaths (all causes)	253	197	
number of deaths resulting from adverse events	44	40	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) ACUTE LEUKAEMIA			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	5 / 2405 (0.21%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	1 / 3	0 / 3	
ADENOCARCINOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ADENOCARCINOMA GASTRIC			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADENOCARCINOMA OF COLON			
subjects affected / exposed	3 / 2405 (0.12%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADENOCARCINOMA PANCREAS			
subjects affected / exposed	3 / 2405 (0.12%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
BILE DUCT ADENOCARCINOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGIOSARCOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDIX CANCER			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B PRECURSOR TYPE ACUTE LEUKAEMIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			
subjects affected / exposed	9 / 2405 (0.37%)	6 / 2364 (0.25%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
BENIGN BREAST NEOPLASM			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BENIGN NEOPLASM OF SKIN			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAPLASTIC LARGE CELL LYMPHOMA T- AND NULL-CELL TYPES			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CHRONIC LYMPHOCYTIC LEUKAEMIA			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
CLEAR CELL RENAL CELL CARCINOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

COLON CANCER			
subjects affected / exposed	2 / 2405 (0.08%)	6 / 2364 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
BLADDER CANCER			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLADDER TRANSITIONAL CELL CARCINOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE GIANT CELL TUMOUR BENIGN			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHONDROSARCOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST ANGIOSARCOMA			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
BRONCHIAL CARCINOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC MYXOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CERVIX CARCINOMA			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLANGIOCARCINOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BOWEN'S DISEASE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLORECTAL CANCER			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONJUNCTIVAL MELANOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DERMATOFIBROSARCOMA PROTUBERANS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIFFUSE LARGE B-CELL LYMPHOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOMETRIAL ADENOCARCINOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOMETRIAL CANCER			

subjects affected / exposed	4 / 2405 (0.17%)	6 / 2364 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
ESSENTIAL THROMBOCYTHAEMIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOLLICULAR LYMPHOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GANGLIONEUROMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC CANCER			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
GASTRIC NEOPLASM			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
GASTROINTESTINAL CARCINOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
GLIOBLASTOMA			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
METASTATIC MALIGNANT MELANOMA			

subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
LENTIGO MALIGNA			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKAEMIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG ADENOCARCINOMA			
subjects affected / exposed	3 / 2405 (0.12%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
LUNG NEOPLASM			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
LUNG NEOPLASM MALIGNANT			
subjects affected / exposed	5 / 2405 (0.21%)	9 / 2364 (0.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 9	
deaths causally related to treatment / all	0 / 2	0 / 3	
LYMPHOCYTIC LYMPHOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA			
subjects affected / exposed	9 / 2405 (0.37%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA IN SITU			

subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT NEOPLASM OF RENAL PELVIS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
MALIGNANT NEOPLASM OF UNKNOWN PRIMARY SITE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
MALIGNANT PERITONEAL NEOPLASM			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
MENINGIOMA			
subjects affected / exposed	1 / 2405 (0.04%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRADUCTAL PROLIFERATIVE BREAST LESION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTATIC UTERINE CANCER			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
MONOCLONAL GAMMOPATHY			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYELODYSPLASTIC SYNDROME			

subjects affected / exposed	3 / 2405 (0.12%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
MYELOID LEUKAEMIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
NEOPLASM MALIGNANT			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NON-SMALL CELL LUNG CANCER METASTATIC			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NEURILEMMOMA BENIGN			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROENDOCRINE CARCINOMA METASTATIC			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
NEUROENDOCRINE CARCINOMA OF THE SKIN			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROENDOCRINE TUMOUR			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (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			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NEOPLASM OF ORBIT			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL CARCINOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARCOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
OVARIAN EPITHELIAL CANCER			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (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	7 / 2405 (0.29%)	6 / 2364 (0.25%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 5	0 / 3	
PANCREATIC CARCINOMA METASTATIC			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PAPILLARY THYROID CANCER			
subjects affected / exposed	5 / 2405 (0.21%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARATHYROID TUMOUR BENIGN			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC NEOPLASM			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATE CANCER			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL ADENOCARCINOMA			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL CANCER			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL CELL CARCINOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL MELANOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SALIVARY GLAND CANCER			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVARIAN CANCER			

subjects affected / exposed	3 / 2405 (0.12%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
SQUAMOUS CELL CARCINOMA OF THE CERVIX			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF THE TONGUE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THYROID CANCER			
subjects affected / exposed	1 / 2405 (0.04%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
THYROID NEOPLASM			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONGUE NEOPLASM MALIGNANT STAGE UNSPECIFIED			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
TRANSITIONAL CELL CARCINOMA			
subjects affected / exposed	2 / 2405 (0.08%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	3 / 2405 (0.12%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

SECOND PRIMARY MALIGNANCY			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL CELL LUNG CANCER			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
SMALL INTESTINE CARCINOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINE LEIOMYOSARCOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOFT TISSUE SARCOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (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	5 / 2405 (0.21%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE CANCER			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (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 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VULVAL CANCER			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
EMBOLISM			
subjects affected / exposed	3 / 2405 (0.12%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
AXILLARY VEIN THROMBOSIS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VARICOSE VEIN			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOSIS			
subjects affected / exposed	3 / 2405 (0.12%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOPHLEBITIS			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBCLAVIAN VEIN THROMBOSIS			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (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 / 2405 (0.04%)	1 / 2364 (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 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENOUS THROMBOSIS LIMB			
subjects affected / exposed	0 / 2405 (0.00%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	5 / 2405 (0.21%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	4 / 2405 (0.17%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (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	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM VENOUS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
JUGULAR VEIN THROMBOSIS			

subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
SKIN NEOPLASM EXCISION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HOSPITALISATION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST TUMOUR EXCISION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABORTION INDUCED			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (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	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN			

subjects affected / exposed	6 / 2405 (0.25%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	1 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHILLS			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYST			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED THROMBOSIS			
subjects affected / exposed	3 / 2405 (0.12%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	5 / 2405 (0.21%)	7 / 2364 (0.30%)	
occurrences causally related to treatment / all	2 / 5	5 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
NECROSIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERALISED OEDEMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			

subjects affected / exposed	2 / 2405 (0.08%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
MASS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL INFLAMMATION			
subjects affected / exposed	1 / 2405 (0.04%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	5 / 2405 (0.21%)	5 / 2364 (0.21%)	
occurrences causally related to treatment / all	1 / 6	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	46 / 2405 (1.91%)	40 / 2364 (1.69%)	
occurrences causally related to treatment / all	9 / 53	11 / 41	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	3 / 2405 (0.12%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAPHYLACTIC SHOCK			

subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 2405 (0.00%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERSENSITIVITY			
subjects affected / exposed	3 / 2405 (0.12%)	11 / 2364 (0.47%)	
occurrences causally related to treatment / all	2 / 3	6 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
ABNORMAL UTERINE BLEEDING			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST INFLAMMATION			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST PAIN			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CERVICAL POLYP			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAVY MENSTRUAL BLEEDING			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVARIAN CYST			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VAGINAL HAEMORRHAGE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC CYST			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (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			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHMA			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATELECTASIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHIECTASIS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOSPASM			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COUGH			
subjects affected / exposed	2 / 2405 (0.08%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHONIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	7 / 2405 (0.29%)	6 / 2364 (0.25%)	
occurrences causally related to treatment / all	2 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
OROPHARYNGEAL DISCOMFORT			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	1 / 2405 (0.04%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
LUNG CONSOLIDATION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFILTRATION			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NASAL OEDEMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NASAL POLYPS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	4 / 2405 (0.17%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	3 / 2405 (0.12%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			

subjects affected / exposed	5 / 2405 (0.21%)	5 / 2364 (0.21%)	
occurrences causally related to treatment / all	1 / 5	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
PULMONARY FIBROSIS			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
HYPOMANIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANXIETY			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DELUSIONAL DISORDER, UNSPECIFIED TYPE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSION			
subjects affected / exposed	3 / 2405 (0.12%)	5 / 2364 (0.21%)	
occurrences causally related to treatment / all	1 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
MAJOR DEPRESSION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MANIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL DISORDER			

subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERSISTENT DEPRESSIVE DISORDER			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERSONALITY CHANGE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSYCHOTIC DISORDER			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDAL IDEATION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDE ATTEMPT			
subjects affected / exposed	2 / 2405 (0.08%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
REACTIVE PSYCHOSIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
DEVICE DISLOCATION			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE EXTRUSION			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE BREAKAGE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (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	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLANGITIS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (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	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FAILURE			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TROPONIN INCREASED			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
EJECTION FRACTION DECREASED			
subjects affected / exposed	10 / 2405 (0.42%)	14 / 2364 (0.59%)	
occurrences causally related to treatment / all	9 / 10	14 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOGLOBIN DECREASED			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER FUNCTION TEST INCREASED			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	3 / 2405 (0.12%)	7 / 2364 (0.30%)	
occurrences causally related to treatment / all	1 / 3	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD GLUCOSE FLUCTUATION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
CONCUSSION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACCIDENTAL OVERDOSE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANKLE FRACTURE			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
AVULSION FRACTURE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST PROCEDURAL COMPLICATION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILIUM FRACTURE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	2 / 2405 (0.08%)	5 / 2364 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
GRAFT THROMBOSIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FRACTURED SACRUM			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFUSION RELATED REACTION			
subjects affected / exposed	1 / 2405 (0.04%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX TRAUMATIC			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (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	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE FRACTURES			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER LIMB FRACTURE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT DISLOCATION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTENTIONAL OVERDOSE			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTOPERATIVE WOUND COMPLICATION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCEDURAL PAIN			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY RADIATION INJURY			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIATION SKIN INJURY			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	0 / 2405 (0.00%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
TIBIA FRACTURE			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN LACERATION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SHOULDER FRACTURE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEROMA			
subjects affected / exposed	3 / 2405 (0.12%)	0 / 2364 (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	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
RIB FRACTURE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THERMAL BURN			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (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	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
WRIST FRACTURE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
CONGENITAL APLASIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYLORIC STENOSIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ANGINA PECTORIS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	3 / 2405 (0.12%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
ACUTE CORONARY SYNDROME			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL THROMBOSIS			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

AORTIC VALVE DISEASE			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARRHYTHMIA			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (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	6 / 2405 (0.25%)	6 / 2364 (0.25%)	
occurrences causally related to treatment / all	1 / 7	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY STENOSIS			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOGENIC SHOCK			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIOMYOPATHY			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CHRONIC			
subjects affected / exposed	1 / 2405 (0.04%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE ACUTE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	28 / 2405 (1.16%)	44 / 2364 (1.86%)	
occurrences causally related to treatment / all	24 / 31	43 / 48	
deaths causally related to treatment / all	1 / 2	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	3 / 2405 (0.12%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
BRADYCARDIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK SECOND DEGREE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METABOLIC CARDIOMYOPATHY			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MITRAL VALVE DISEASE			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
MITRAL VALVE INCOMPETENCE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	5 / 2405 (0.21%)	5 / 2364 (0.21%)	
occurrences causally related to treatment / all	1 / 5	2 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
PALPITATIONS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE HEART DISEASE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS NODE DYSFUNCTION			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY THROMBOSIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DILATED CARDIOMYOPATHY			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EXTRASYSTOLES			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS BRADYCARDIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR HYPOKINESIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (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	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR ARRHYTHMIA			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (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	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STRESS CARDIOMYOPATHY			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
ATAXIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
AUTONOMIC NERVOUS SYSTEM IMBALANCE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 2405 (0.00%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
CEREBRAL INFARCTION			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERCOSTAL NEURALGIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLIC STROKE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAD TITUBATION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRACRANIAL ANEURYSM			

subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (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	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (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	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEURALGIC AMYOTROPHY			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	0 / 2405 (0.00%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAESTHESIA			
subjects affected / exposed	1 / 2405 (0.04%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
PERIPHERAL SENSORY NEUROPATHY			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSYCHOGENIC SEIZURE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCIATICA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	1 / 2405 (0.04%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROTOXICITY			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUNCT SYNDROME			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	5 / 2405 (0.21%)	13 / 2364 (0.55%)	
occurrences causally related to treatment / all	1 / 5	2 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
THALAMIC INFARCTION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			

subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRIGEMINAL NEURALGIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
AGRANULOCYTOSIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAEMIA			
subjects affected / exposed	8 / 2405 (0.33%)	10 / 2364 (0.42%)	
occurrences causally related to treatment / all	5 / 10	7 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE BONE MARROW APLASIA			
subjects affected / exposed	8 / 2405 (0.33%)	9 / 2364 (0.38%)	
occurrences causally related to treatment / all	1 / 9	3 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	196 / 2405 (8.15%)	211 / 2364 (8.93%)	
occurrences causally related to treatment / all	18 / 215	29 / 239	
deaths causally related to treatment / all	0 / 0	0 / 1	
IDIOPATHIC CYTOPENIA OF UNDETERMINED SIGNIFICANCE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOLYTIC ANAEMIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			

subjects affected / exposed	5 / 2405 (0.21%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHADENOPATHY			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (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	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	4 / 2405 (0.17%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYELOSUPPRESSION			
subjects affected / exposed	3 / 2405 (0.12%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	34 / 2405 (1.41%)	25 / 2364 (1.06%)	
occurrences causally related to treatment / all	4 / 39	3 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
EXTERNAL EAR INFLAMMATION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN HEARING LOSS			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TYMPANIC MEMBRANE PERFORATION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VERTIGO			
subjects affected / exposed	4 / 2405 (0.17%)	5 / 2364 (0.21%)	
occurrences causally related to treatment / all	0 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
VESTIBULAR DISORDER			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
PAPILLOEDEMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VISUAL ACUITY REDUCED			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VISUAL FIELD DEFECT			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OPTIC NERVE DISORDER			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

COLITIS			
subjects affected / exposed	5 / 2405 (0.21%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	1 / 5	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	7 / 2405 (0.29%)	6 / 2364 (0.25%)	
occurrences causally related to treatment / all	1 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	3 / 2405 (0.12%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL HAEMORRHAGE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	2 / 2405 (0.08%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	1 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	18 / 2405 (0.75%)	58 / 2364 (2.45%)	
occurrences causally related to treatment / all	8 / 18	26 / 67	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULUM INTESTINAL HAEMORRHAGIC			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL PERFORATION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER PERFORATION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL HERNIA STRANGULATED			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER HAEMORRHAGE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			

subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (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	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL PERFORATION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
GASTROINTESTINAL TOXICITY			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL PAIN			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHOIDS			

subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL ISCHAEMIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
NEUTROPENIC COLITIS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRA-ABDOMINAL HAEMATOMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTUSSUSCEPTION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER GASTROINTESTINAL HAEMORRHAGE			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	14 / 2405 (0.58%)	18 / 2364 (0.76%)	
occurrences causally related to treatment / all	0 / 16	2 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA MOUTH			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL PAIN			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (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	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	3 / 2405 (0.12%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCTITIS			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	15 / 2405 (0.62%)	19 / 2364 (0.80%)	
occurrences causally related to treatment / all	2 / 21	1 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	1 / 2405 (0.04%)	7 / 2364 (0.30%)	
occurrences causally related to treatment / all	0 / 1	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBILEUS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOOTHACHE			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			

subjects affected / exposed	1 / 2405 (0.04%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ERYTHEMA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE FEBRILE NEUTROPHILIC DERMATOSIS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGIOEDEMA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DERMATITIS ACNEIFORM			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DERMATITIS EXFOLIATIVE GENERALISED			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	1 / 2405 (0.04%)	5 / 2364 (0.21%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

URTICARIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXIC SKIN ERUPTION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN ULCER			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (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 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MACULAR			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL IMPAIRMENT			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE KIDNEY INJURY			
subjects affected / exposed	2 / 2405 (0.08%)	5 / 2364 (0.21%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSURIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL COLIC			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETERIC OBSTRUCTION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETEROLITHIASIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY INCONTINENCE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
GOITRE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTHYROIDISM			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THYROID DISORDER			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SJOGREN'S SYNDROME			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYALGIA			
subjects affected / exposed	3 / 2405 (0.12%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS OF JAW			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROTATOR CUFF SYNDROME			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (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			
ACUTE HEPATITIS B			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL ABSCESS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL INFECTION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (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	3 / 2405 (0.12%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS ORAL			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (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	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANORECTAL INFECTION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS PERFORATED			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERAEMIA			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERIAL INFECTION			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE INFECTION			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST CELLULITIS			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	3 / 2405 (0.12%)	7 / 2364 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	13 / 2405 (0.54%)	15 / 2364 (0.63%)	
occurrences causally related to treatment / all	2 / 13	2 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC SINUSITIS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM COLITIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST ABSCESS			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			

subjects affected / exposed	3 / 2405 (0.12%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER DISSEMINATED			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (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 / 2405 (0.04%)	1 / 2364 (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	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	6 / 2405 (0.25%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS INTESTINAL PERFORATED			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOCARDITIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	2 / 2405 (0.08%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA INFECTION			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	3 / 2405 (0.12%)	8 / 2364 (0.34%)	
occurrences causally related to treatment / all	0 / 3	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 INFLUENZA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS B REACTIVATION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED SEPSIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (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	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED SEROMA			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	6 / 2405 (0.25%)	7 / 2364 (0.30%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARYNGITIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC SEPSIS			
subjects affected / exposed	4 / 2405 (0.17%)	11 / 2364 (0.47%)	
occurrences causally related to treatment / all	2 / 4	4 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOCALISED INFECTION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 2405 (0.12%)	4 / 2364 (0.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHANGITIS			

subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MASTITIS			
subjects affected / exposed	4 / 2405 (0.17%)	4 / 2364 (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	0 / 2405 (0.00%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC INFECTION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARYNGOPHARYNGITIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OTITIS MEDIA ACUTE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARONYCHIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIODONTITIS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONSILLAR ABSCESS			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
PHLEBITIS INFECTIVE			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL INFECTION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	27 / 2405 (1.12%)	19 / 2364 (0.80%)	
occurrences causally related to treatment / all	3 / 28	5 / 19	
deaths causally related to treatment / all	0 / 1	0 / 0	
PHARYNGITIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA BACTERIAL			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA PNEUMOCOCCAL			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (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	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA STREPTOCOCCAL			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTOPERATIVE ABSCESS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PYELONEPHRITIS			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS ACUTE			
subjects affected / exposed	2 / 2405 (0.08%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL ABSCESS			

subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 2405 (0.08%)	2 / 2364 (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	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	9 / 2405 (0.37%)	7 / 2364 (0.30%)	
occurrences causally related to treatment / all	1 / 11	1 / 7	
deaths causally related to treatment / all	0 / 1	1 / 1	
PSEUDOMONAL BACTERAEMIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SERRATIA INFECTION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUSITIS			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN INFECTION			
subjects affected / exposed	5 / 2405 (0.21%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOFT TISSUE INFECTION			

subjects affected / exposed	0 / 2405 (0.00%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL SKIN INFECTION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STREPTOCOCCAL BACTERAEMIA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONSILLITIS			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (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	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR DEVICE INFECTION			
subjects affected / exposed	6 / 2405 (0.25%)	3 / 2364 (0.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VARICELLA			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	1 / 2405 (0.04%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	9 / 2405 (0.37%)	8 / 2364 (0.34%)	
occurrences causally related to treatment / all	1 / 10	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	8 / 2405 (0.33%)	9 / 2364 (0.38%)	
occurrences causally related to treatment / all	0 / 8	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
VULVAL ABSCESS			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			

subjects affected / exposed	2 / 2405 (0.08%)	5 / 2364 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 2405 (0.00%)	6 / 2364 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	5 / 2405 (0.21%)	19 / 2364 (0.80%)	
occurrences causally related to treatment / all	1 / 5	4 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ELECTROLYTE IMBALANCE			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	2 / 2405 (0.08%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			

subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HYPOCALCAEMIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			
subjects affected / exposed	0 / 2405 (0.00%)	2 / 2364 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	2 / 2405 (0.08%)	8 / 2364 (0.34%)	
occurrences causally related to treatment / all	1 / 2	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOMAGNESAEMIA			
subjects affected / exposed	1 / 2405 (0.04%)	5 / 2364 (0.21%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLUID RETENTION			
subjects affected / exposed	1 / 2405 (0.04%)	0 / 2364 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 2405 (0.00%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOVOLAEMIA			
subjects affected / exposed	1 / 2405 (0.04%)	1 / 2364 (0.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR LYSIS SYNDROME			

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

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

Non-serious adverse events	Placebo + Trastuzumab + Chemotherapy	Pertuzumab + Trastuzumab + Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2374 / 2405 (98.71%)	2353 / 2364 (99.53%)	
Vascular disorders			
LYMPHOEDEMA			
subjects affected / exposed	164 / 2405 (6.82%)	137 / 2364 (5.80%)	
occurrences (all)	169	140	
HYPERTENSION			
subjects affected / exposed	123 / 2405 (5.11%)	95 / 2364 (4.02%)	
occurrences (all)	131	107	
HOT FLUSH			
subjects affected / exposed	518 / 2405 (21.54%)	492 / 2364 (20.81%)	
occurrences (all)	574	532	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	502 / 2405 (20.87%)	515 / 2364 (21.79%)	
occurrences (all)	917	958	
FATIGUE			
subjects affected / exposed	1074 / 2405 (44.66%)	1160 / 2364 (49.07%)	
occurrences (all)	1629	1779	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	120 / 2405 (4.99%)	126 / 2364 (5.33%)	
occurrences (all)	152	158	
MUCOSAL INFLAMMATION			
subjects affected / exposed	458 / 2405 (19.04%)	555 / 2364 (23.48%)	
occurrences (all)	600	751	
OEDEMA			

subjects affected / exposed	155 / 2405 (6.44%)	141 / 2364 (5.96%)	
occurrences (all)	176	162	
PAIN			
subjects affected / exposed	164 / 2405 (6.82%)	160 / 2364 (6.77%)	
occurrences (all)	200	189	
PYREXIA			
subjects affected / exposed	439 / 2405 (18.25%)	455 / 2364 (19.25%)	
occurrences (all)	617	646	
OEDEMA PERIPHERAL			
subjects affected / exposed	491 / 2405 (20.42%)	406 / 2364 (17.17%)	
occurrences (all)	588	494	
Reproductive system and breast disorders			
BREAST PAIN			
subjects affected / exposed	110 / 2405 (4.57%)	122 / 2364 (5.16%)	
occurrences (all)	119	136	
Respiratory, thoracic and mediastinal disorders			
RHINORRHOEA			
subjects affected / exposed	136 / 2405 (5.65%)	192 / 2364 (8.12%)	
occurrences (all)	151	210	
OROPHARYNGEAL PAIN			
subjects affected / exposed	176 / 2405 (7.32%)	219 / 2364 (9.26%)	
occurrences (all)	203	260	
EPISTAXIS			
subjects affected / exposed	329 / 2405 (13.68%)	433 / 2364 (18.32%)	
occurrences (all)	417	518	
DYSPNOEA			
subjects affected / exposed	272 / 2405 (11.31%)	284 / 2364 (12.01%)	
occurrences (all)	321	331	
COUGH			
subjects affected / exposed	357 / 2405 (14.84%)	377 / 2364 (15.95%)	
occurrences (all)	445	473	
Psychiatric disorders			
INSOMNIA			

subjects affected / exposed	410 / 2405 (17.05%)	412 / 2364 (17.43%)	
occurrences (all)	466	465	
ANXIETY			
subjects affected / exposed	117 / 2405 (4.86%)	162 / 2364 (6.85%)	
occurrences (all)	121	176	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	246 / 2405 (10.23%)	230 / 2364 (9.73%)	
occurrences (all)	329	293	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	161 / 2405 (6.69%)	152 / 2364 (6.43%)	
occurrences (all)	214	183	
EJECTION FRACTION DECREASED			
subjects affected / exposed	212 / 2405 (8.81%)	175 / 2364 (7.40%)	
occurrences (all)	272	212	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	329 / 2405 (13.68%)	325 / 2364 (13.75%)	
occurrences (all)	701	694	
WEIGHT DECREASED			
subjects affected / exposed	83 / 2405 (3.45%)	197 / 2364 (8.33%)	
occurrences (all)	88	208	
WEIGHT INCREASED			
subjects affected / exposed	137 / 2405 (5.70%)	62 / 2364 (2.62%)	
occurrences (all)	147	64	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	208 / 2405 (8.65%)	235 / 2364 (9.94%)	
occurrences (all)	493	573	
Injury, poisoning and procedural complications			
RADIATION SKIN INJURY			
subjects affected / exposed	261 / 2405 (10.85%)	297 / 2364 (12.56%)	
occurrences (all)	265	304	
Nervous system disorders			

DIZZINESS subjects affected / exposed occurrences (all)	281 / 2405 (11.68%) 365	272 / 2364 (11.51%) 349	
TASTE DISORDER subjects affected / exposed occurrences (all)	175 / 2405 (7.28%) 193	205 / 2364 (8.67%) 231	
PERIPHERAL SENSORY NEUROPATHY subjects affected / exposed occurrences (all)	422 / 2405 (17.55%) 485	427 / 2364 (18.06%) 504	
DYSGEUSIA subjects affected / exposed occurrences (all)	352 / 2405 (14.64%) 481	419 / 2364 (17.72%) 512	
HEADACHE subjects affected / exposed occurrences (all)	569 / 2405 (23.66%) 811	539 / 2364 (22.80%) 798	
NEUROPATHY PERIPHERAL subjects affected / exposed occurrences (all)	373 / 2405 (15.51%) 421	372 / 2364 (15.74%) 431	
PARAESTHESIA subjects affected / exposed occurrences (all)	244 / 2405 (10.15%) 281	279 / 2364 (11.80%) 342	
Blood and lymphatic system disorders NEUTROPENIA subjects affected / exposed occurrences (all)	556 / 2405 (23.12%) 1007	592 / 2364 (25.04%) 1039	
LEUKOPENIA subjects affected / exposed occurrences (all)	235 / 2405 (9.77%) 535	220 / 2364 (9.31%) 484	
ANAEMIA subjects affected / exposed occurrences (all)	567 / 2405 (23.58%) 717	667 / 2364 (28.21%) 833	
Eye disorders LACRIMATION INCREASED			

subjects affected / exposed	324 / 2405 (13.47%)	312 / 2364 (13.20%)	
occurrences (all)	347	334	
DRY EYE			
subjects affected / exposed	113 / 2405 (4.70%)	141 / 2364 (5.96%)	
occurrences (all)	118	146	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	261 / 2405 (10.85%)	285 / 2364 (12.06%)	
occurrences (all)	337	369	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	220 / 2405 (9.15%)	244 / 2364 (10.32%)	
occurrences (all)	297	304	
HAEMORRHOIDS			
subjects affected / exposed	126 / 2405 (5.24%)	186 / 2364 (7.87%)	
occurrences (all)	140	218	
GASTROESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	110 / 2405 (4.57%)	124 / 2364 (5.25%)	
occurrences (all)	124	144	
DYSPEPSIA			
subjects affected / exposed	341 / 2405 (14.18%)	328 / 2364 (13.87%)	
occurrences (all)	406	378	
DRY MOUTH			
subjects affected / exposed	140 / 2405 (5.82%)	150 / 2364 (6.35%)	
occurrences (all)	176	166	
DIARRHOEA			
subjects affected / exposed	1091 / 2405 (45.36%)	1667 / 2364 (70.52%)	
occurrences (all)	1791	3368	
CONSTIPATION			
subjects affected / exposed	762 / 2405 (31.68%)	692 / 2364 (29.27%)	
occurrences (all)	1117	1028	
NAUSEA			
subjects affected / exposed	1582 / 2405 (65.78%)	1639 / 2364 (69.33%)	
occurrences (all)	2900	2960	
VOMITING			

subjects affected / exposed	727 / 2405 (30.23%)	771 / 2364 (32.61%)	
occurrences (all)	1178	1231	
STOMATITIS			
subjects affected / exposed	574 / 2405 (23.87%)	666 / 2364 (28.17%)	
occurrences (all)	828	996	
Skin and subcutaneous tissue disorders			
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	159 / 2405 (6.61%)	220 / 2364 (9.31%)	
occurrences (all)	170	241	
NAIL DISORDER			
subjects affected / exposed	283 / 2405 (11.77%)	283 / 2364 (11.97%)	
occurrences (all)	299	302	
NAIL DISCOLOURATION			
subjects affected / exposed	178 / 2405 (7.40%)	176 / 2364 (7.45%)	
occurrences (all)	181	184	
ERYTHEMA			
subjects affected / exposed	224 / 2405 (9.31%)	241 / 2364 (10.19%)	
occurrences (all)	282	283	
DRY SKIN			
subjects affected / exposed	274 / 2405 (11.39%)	315 / 2364 (13.32%)	
occurrences (all)	297	351	
RASH			
subjects affected / exposed	495 / 2405 (20.58%)	618 / 2364 (26.14%)	
occurrences (all)	646	802	
PRURITUS			
subjects affected / exposed	223 / 2405 (9.27%)	342 / 2364 (14.47%)	
occurrences (all)	281	415	
ALOPECIA			
subjects affected / exposed	1635 / 2405 (67.98%)	1594 / 2364 (67.43%)	
occurrences (all)	1647	1601	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			

subjects affected / exposed	867 / 2405 (36.05%)	765 / 2364 (32.36%)	
occurrences (all)	1259	1029	
BACK PAIN			
subjects affected / exposed	241 / 2405 (10.02%)	213 / 2364 (9.01%)	
occurrences (all)	272	254	
BONE PAIN			
subjects affected / exposed	258 / 2405 (10.73%)	228 / 2364 (9.64%)	
occurrences (all)	348	290	
MUSCLE SPASMS			
subjects affected / exposed	125 / 2405 (5.20%)	221 / 2364 (9.35%)	
occurrences (all)	152	274	
MYALGIA			
subjects affected / exposed	716 / 2405 (29.77%)	620 / 2364 (26.23%)	
occurrences (all)	975	829	
PAIN IN EXTREMITY			
subjects affected / exposed	257 / 2405 (10.69%)	237 / 2364 (10.03%)	
occurrences (all)	315	276	
Infections and infestations			
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	175 / 2405 (7.28%)	184 / 2364 (7.78%)	
occurrences (all)	225	227	
CONJUNCTIVITIS			
subjects affected / exposed	130 / 2405 (5.41%)	151 / 2364 (6.39%)	
occurrences (all)	136	165	
RHINITIS			
subjects affected / exposed	120 / 2405 (4.99%)	144 / 2364 (6.09%)	
occurrences (all)	135	169	
NASOPHARYNGITIS			
subjects affected / exposed	292 / 2405 (12.14%)	323 / 2364 (13.66%)	
occurrences (all)	425	482	
URINARY TRACT INFECTION			
subjects affected / exposed	161 / 2405 (6.69%)	185 / 2364 (7.83%)	
occurrences (all)	195	234	
Metabolism and nutrition disorders			

DECREASED APPETITE			
subjects affected / exposed	488 / 2405 (20.29%)	570 / 2364 (24.11%)	
occurrences (all)	756	936	
HYPOKALAEMIA			
subjects affected / exposed	97 / 2405 (4.03%)	151 / 2364 (6.39%)	
occurrences (all)	112	193	
HYPOMAGNESAEMIA			
subjects affected / exposed	79 / 2405 (3.28%)	146 / 2364 (6.18%)	
occurrences (all)	95	178	

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).
30 September 2021	Protocol BO25126 was amended to Version E to extend the follow up period of the study by an additional 5 years, and to define the required assessments during this extended follow-up. Furthermore, in the interest of gathering key safety data, study treatment related serious adverse events (SAEs), primary cardiac events and survival status were also to be collected in this patient population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported