Clinical trial results:
Multicenter Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC-T) With Doxorubicin and Cyclophosphamide Followed by Docetaxel and Trastuzumab (Herceptin®) (AC-TH) and With Docetaxel, Carboplatin and Trastuzumab (TCH) in the Adjuvant Treatment of Node Positive and High Risk Node Negative Patients With Operable Breast Cancer Containing the HER2 Alteration

Summary

EudraCT number	2008-005127-29
Trial protocol	HU SK
Global end of trial date	30 December 2014

Results information

Result version number	v1 (current)
This version publication date	02 July 2016
First version publication date	02 July 2016

Trial information

Trial identification

Sponsor protocol code	TAX_GMA_302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00021255
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	17 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare disease-free survival after treatment with doxorubicin and cyclophosphamide followed by docetaxel (Taxotere®) (AC-T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (Herceptin®) (AC-TH) and with docetaxel in combination with carboplatin and Herceptin® (TCH) in the adjuvant treatment of node positive and high risk node negative subjects with operable breast cancer containing the human epidermal growth factor receptor 2 (HER2) alteration.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 April 2001
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hong Kong: 18
Country: Number of subjects enrolled	India: 18
Country: Number of subjects enrolled	Korea, Republic of: 64
Country: Number of subjects enrolled	Taiwan: 57
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 68
Country: Number of subjects enrolled	Bosnia and Herzegovina: 3
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Croatia: 41
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Estonia: 11
Country: Number of subjects enrolled	France: 129
Country: Number of subjects enrolled	Germany: 313
Country: Number of subjects enrolled	Greece: 2

Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Ireland: 129
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Poland: 260
Country: Number of subjects enrolled	Romania: 35
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Slovakia: 20
Country: Number of subjects enrolled	Slovenia: 22
Country: Number of subjects enrolled	Spain: 90
Country: Number of subjects enrolled	Sweden: 29
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Cyprus: 3
Country: Number of subjects enrolled	Egypt: 17
Country: Number of subjects enrolled	Israel: 61
Country: Number of subjects enrolled	Lebanon: 42
Country: Number of subjects enrolled	Tunisia: 4
Country: Number of subjects enrolled	Canada: 143
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	United States: 990
Country: Number of subjects enrolled	Australia: 293
Country: Number of subjects enrolled	New Zealand: 32
Country: Number of subjects enrolled	South Africa: 49
Country: Number of subjects enrolled	Argentina: 23
Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Uruguay: 7
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 4
Worldwide total number of subjects	3222
EEA total number of subjects	1315

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)	3028
From 65 to 84 years	194
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 433 centers in 43 countries. A total of 3222 subjects were randomized between 05 April 2001 and 30 March 2004.

Pre-assignment

Screening details:

Subjects were stratified according to institution, nodal status (negative, positive 1-3 nodes, positive 4 or more nodes), hormonal receptor status (estrogen and/or progesterone receptor positive versus negative) and randomized in 1:1:1 ratio to receive adjuvant therapy with either AC T, AC TH or TCH.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)

Arm description:

Doxorubicin in combination with cyclophosphamide on Day 1 of every 3 weeks for 4 cycles followed by docetaxel every 3 weeks for another 4 cycles.

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

Dosage and administration details:

Doxorubicin 60 mg/m² over 5-15 minutes by intravenous (IV) bolus injection every 3 weeks.

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

Dosage and administration details:

Cyclophosphamide 600 mg/m² over 5-60 minutes by IV bolus injection every 3 weeks.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere®
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel 100 mg/m² over 1 hour by IV infusion every 3 weeks.

Arm title	AC Followed by Docetaxel + Herceptin (ACTH)

Arm description:

Doxorubicin in combination with cyclophosphamide on Day 1 of every 3 weeks for 4 cycles. Herceptin on Day 1 of Cycle 5, followed by Herceptin weekly starting from Day 8; and docetaxel on Day 2 of Cycle 5, then on Day 1 of every 3 weeks for all subsequent cycles (total 4 cycles). After completion of the last

cycle of chemotherapy, Herceptin infusion was administered every 3 weeks until 1 year from date of initial Herceptin dose.

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

Dosage and administration details:

Doxorubicin 60 mg/m²over 5-15 minutes by IV bolus injection every 3 weeks.

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

Dosage and administration details:

Cyclophosphamide 600 mg/m² over 5-60 minutes by IV bolus injection every 3 weeks.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere®
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel 100 mg/m² over 1 hour by IV infusion on day 2 for the first cycle and on day 1 for all subsequent cycles.

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

Dosage and administration details:

Herceptin 4 mg/kg by IV infusion over 90 minutes on Day 1 followed by Herceptin 2 mg/kg by IV infusion over 30 minutes on Day 8 and 15 respectively. After completion of the last cycle, subjects received Herceptin 6 mg/kg over 30 minutes by IV infusion every 3 weeks until 1 year from date of initial Herceptin dose.

Arm title	Docetaxel + Carboplatin + Herceptin (TCH)

Arm description:

Herceptin on Day 1 of Cycle 1 only, followed by Herceptin weekly starting from Day 8 until three weeks after the last cycle of chemotherapy. Docetaxel on Day 2 of Cycle 1, then on Day 1 of all subsequent cycles followed by carboplatin repeated every 3 weeks for a total of 6 cycles. After completion of the last cycle of chemotherapy, Herceptin was administered every 3 weeks until 1 year from date of initial Herceptin dose.

Arm type	Experimental
Investigational medicinal product name	Herceptin®
Investigational medicinal product code	
Other name	Trastuzumab
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Herceptin 4 mg/kg by IV infusion over 90 minutes on Day 1 and 2 mg/kg by IV infusion over 30 minutes on Day 8 and 15 respectively for first cycle. Herceptin 2 mg/kg by IV infusion over 30 minutes on Day1, 8 and 15 for all subsequent cycles. After completion of the last cycle, Herceptin 6 mg/kg by IV infusion over 30 minutes was given every 3 weeks until 1 year from date of initial Herceptin dose.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere®
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel 75 mg/m² by IV infusion over 1 hour on Day 2 for the first cycle and on Day 1 for all subsequent cycles.

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

Dosage and administration details:

Carboplatin at target AUC = 6 mg/mL/min by IV infusion over 30-60 minutes on Day 2 for the first cycle and on Day 1 for all subsequent cycles.

Number of subjects in period 1	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)	AC Followed by Docetaxel + Herceptin (ACTH)	Docetaxel + Carboplatin + Herceptin (TCH)
Started	1073	1074	1075
Treated	1045	1072	1057
Completed	952	804	926
Not completed	121	270	149
Other than specified above	-	38	19
Second primary malignancy	-	4	1
Herceptin toxicity	-	22	6
Adverse Event	46	30	18
Randomized but not treated	28	2	18
Death	1	-	2
Breast cancer relapse	5	18	11
Lost to Follow-up	-	2	3
Withdrawal by Subject	41	64	26
Protocol Violation	-	2	-
Cardiac toxicity	-	61	32
Missing	-	27	13

Baseline characteristics

Reporting groups	
Reporting group title	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)

Reporting group description:

Doxorubicin in combination with cyclophosphamide on Day 1 of every 3 weeks for 4 cycles followed by docetaxel every 3 weeks for another 4 cycles.

Reporting group title	AC Followed by Docetaxel + Herceptin (ACTH)

Reporting group description:

Doxorubicin in combination with cyclophosphamide on Day 1 of every 3 weeks for 4 cycles. Herceptin on Day 1 of Cycle 5, followed by Herceptin weekly starting from Day 8; and docetaxel on Day 2 of Cycle 5, then on Day 1 of every 3 weeks for all subsequent cycles (total 4 cycles). After completion of the last cycle of chemotherapy, Herceptin infusion was administered every 3 weeks until 1 year from date of initial Herceptin dose.

Reporting group title	Docetaxel + Carboplatin + Herceptin (TCH)

Reporting group description:

Herceptin on Day 1 of Cycle 1 only, followed by Herceptin weekly starting from Day 8 until three weeks after the last cycle of chemotherapy. Docetaxel on Day 2 of Cycle 1, then on Day 1 of all subsequent cycles followed by carboplatin repeated every 3 weeks for a total of 6 cycles. After completion of the last cycle of chemotherapy, Herceptin was administered every 3 weeks until 1 year from date of initial Herceptin dose.

Reporting group values	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)	AC Followed by Docetaxel + Herceptin (ACTH)	Docetaxel + Carboplatin + Herceptin (TCH)
Number of subjects	1073	1074	1075
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	48.8	48.7	48.6
standard deviation	± 9.7	± 9.7	± 9.9
Gender categorical			
Units: Subjects			
Female	1073	1074	1075
Male	0	0	0

Reporting group values	Total		
Number of subjects	3222		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	3222		
Male	0		

End points

End points reporting groups

Reporting group title	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)

Reporting group description:

Doxorubicin in combination with cyclophosphamide on Day 1 of every 3 weeks for 4 cycles followed by docetaxel every 3 weeks for another 4 cycles.

Reporting group title	AC Followed by Docetaxel + Herceptin (ACTH)

Reporting group description:

Doxorubicin in combination with cyclophosphamide on Day 1 of every 3 weeks for 4 cycles. Herceptin on Day 1 of Cycle 5, followed by Herceptin weekly starting from Day 8; and docetaxel on Day 2 of Cycle 5, then on Day 1 of every 3 weeks for all subsequent cycles (total 4 cycles). After completion of the last cycle of chemotherapy, Herceptin infusion was administered every 3 weeks until 1 year from date of initial Herceptin dose.

Reporting group title	Docetaxel + Carboplatin + Herceptin (TCH)

Reporting group description:

Herceptin on Day 1 of Cycle 1 only, followed by Herceptin weekly starting from Day 8 until three weeks after the last cycle of chemotherapy. Docetaxel on Day 2 of Cycle 1, then on Day 1 of all subsequent cycles followed by carboplatin repeated every 3 weeks for a total of 6 cycles. After completion of the last cycle of chemotherapy, Herceptin was administered every 3 weeks until 1 year from date of initial Herceptin dose.

Primary: Percentage of Subjects With Disease Free Survival at 5 Years

End point title	Percentage of Subjects With Disease Free Survival at 5 Years[1]

End point description:

Disease Free Survival was defined as the interval from the date of randomization to the date of local, regional or metastatic relapse or the date of second primary cancer (with the exception of curatively treated non-melanoma skin cancer or in situ carcinoma of the cervix) or death from any cause whichever occured first. Disease free survival was estimated using the Kaplan-Meier method. Analysis was performed on Intent-To-Treat (ITT) population that included all randomized subjects.

End point type	Primary

End point timeframe:

From randomization until relapse or death or up to 5 years.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analyses were performed: “Kaplan-Meier analysis, including landmark estimates of 1- to 10-year survival probabilities, median times and graph was performed”.

End point values	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)	AC Followed by Docetaxel + Herceptin (ACTH)	Docetaxel + Carboplatin + Herceptin (TCH)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1073	1074	1074	
Units: Percentage of Subjects				
number (confidence interval 95%)	75.5 (72.8 to 78.2)	83.2 (80.9 to 85.4)	81 (78.6 to 83.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease Free Survival at 10 Years

End point title	Percentage of Subjects With Disease Free Survival at 10 Years

End point description:

Disease free survival was defined as the interval from the date of randomization to the date of local, regional or metastatic relapse or the date of second primary cancer (with the exception of curatively treated non-melanoma skin cancer or in situ carcinoma of the cervix) or death from any cause whichever occured first. Disease free survival was estimated using the Kaplan-Meier method. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomization until relapse or death or up to 10 years.

End point values	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)	AC Followed by Docetaxel + Herceptin (ACTH)	Docetaxel + Carboplatin + Herceptin (TCH)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1073	1074	1075	
Units: Percentage of Subjects				
number (confidence interval 95%)	67.2 (64.2 to 70.2)	73.4 (70.6 to 76.2)	72.3 (69.4 to 75.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival- Percentage of Subjects who Survived at 10 Years

End point title	Overall Survival- Percentage of Subjects who Survived at 10 Years

End point description:

Overall survival of the subjects was measured from the date of randomization up to the date of death due to any cause. Overall survival was estimated using the Kaplan-Meier method. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From randomization until death or up to 10 years

End point values	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)	AC Followed by Docetaxel + Herceptin (ACTH)	Docetaxel + Carboplatin + Herceptin (TCH)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1073	1074	1075	
Units: Percentage of Subjects				
number (confidence interval 95%)	78.9 (76.2 to 81.5)	86 (83.8 to 88.2)	83.4 (81 to 85.8)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from the time the subject started treatment with study drug until 30 days after the last infusion of study treatment (chemotherapy or Herceptin)

Adverse event reporting additional description:

Reported AEs & deaths are treatment-emergent that is AEs that developed/worsened & deaths that occurred during 'on treatment period' (from first infusion of study drug until 30 days after last infusion of study drug). Safety population included all treated subjects. Source vocabulary used to define AE term: Pooled NCI-CTC v 2.0 and COSTART v 5.0

Assessment type	Systematic

Dictionary used

Dictionary name	NCI V2/COSTART V5
Dictionary version	2/5

Reporting groups

Reporting group title	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)

Reporting group description:

Doxorubicin in combination with cyclophosphamide on Day 1 of every 3 weeks for 4 cycles followed by docetaxel every 3 weeks for another 4 cycles.

Reporting group title	Docetaxel + Carboplatin + Herceptin (TCH)

Reporting group description:

Herceptin on Day 1 of Cycle 1 only, followed by Herceptin weekly starting from Day 8 until three weeks after the last cycle of chemotherapy. Docetaxel on Day 2 of Cycle 1, then on Day 1 of all subsequent cycles followed by carboplatin repeated every 3 weeks for a total of 6 cycles. After completion of the last cycle of chemotherapy, Herceptin was administered every 3 weeks until 1 year from date of initial Herceptin dose.

Reporting group title	AC Followed by Docetaxel + Herceptin (ACTH)

Reporting group description:

Doxorubicin in combination with cyclophosphamide on Day 1 of every 3 weeks for 4 cycles. Herceptin on Day 1 of Cycle 5, followed by Herceptin weekly starting from Day 8; and docetaxel on Day 2 of Cycle 5, then on Day 1 of every 3 weeks for all subsequent cycles (total 4 cycles). After completion of the last cycle of chemotherapy, Herceptin infusion was administered every 3 weeks until 1 year from date of initial Herceptin dose.

Serious adverse events	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)	Docetaxel + Carboplatin + Herceptin (TCH)	AC Followed by Docetaxel + Herceptin (ACTH)
Total subjects affected by serious adverse events			
subjects affected / exposed	218 / 1018 (21.41%)	283 / 1056 (26.80%)	298 / 1100 (27.09%)
number of deaths (all causes)	194	163	148
number of deaths resulting from adverse events			
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Aortic Stenosis			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	2 / 1018 (0.20%)	3 / 1056 (0.28%)	3 / 1100 (0.27%)
occurrences causally related to treatment / all	1 / 3	2 / 4	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial Anomaly			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Av Block			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	2 / 1100 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular Disorder			
subjects affected / exposed	2 / 1018 (0.20%)	0 / 1056 (0.00%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid Occlusion			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	0 / 1018 (0.00%)	3 / 1056 (0.28%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep Thrombophlebitis			

subjects affected / exposed	6 / 1018 (0.59%)	15 / 1056 (1.42%)	13 / 1100 (1.18%)
occurrences causally related to treatment / all	4 / 9	5 / 19	2 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram Abnormal			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart Arrest			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	2 / 1100 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Heart Failure			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage			
subjects affected / exposed	0 / 1018 (0.00%)	2 / 1056 (0.19%)	2 / 1100 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Heart Failure			
subjects affected / exposed	8 / 1018 (0.79%)	2 / 1056 (0.19%)	25 / 1100 (2.27%)
occurrences causally related to treatment / all	1 / 10	2 / 3	6 / 39
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial Ischemia			

subjects affected / exposed	0 / 1018 (0.00%)	4 / 1056 (0.38%)	5 / 1100 (0.45%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitation			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	3 / 1100 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial Effusion			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postural Hypotension			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 1018 (0.10%)	1 / 1056 (0.09%)	4 / 1100 (0.36%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tachycardia			
subjects affected / exposed	2 / 1018 (0.20%)	2 / 1056 (0.19%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitis			

subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Arrhythmia			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Anxiety			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral Infarct			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Confusion			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 1018 (0.00%)	3 / 1056 (0.28%)	5 / 1100 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emotional Lability			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	2 / 1100 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand Mal Convulsion			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy			
subjects affected / exposed	3 / 1018 (0.29%)	4 / 1056 (0.38%)	3 / 1100 (0.27%)
occurrences causally related to treatment / all	3 / 4	4 / 7	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trismus			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 1018 (0.00%)	2 / 1056 (0.19%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 1018 (0.10%)	9 / 1056 (0.85%)	8 / 1100 (0.73%)
occurrences causally related to treatment / all	1 / 1	9 / 11	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			

subjects affected / exposed	21 / 1018 (2.06%)	20 / 1056 (1.89%)	23 / 1100 (2.09%)
occurrences causally related to treatment / all	24 / 24	19 / 22	27 / 28
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphedema			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 1018 (0.10%)	2 / 1056 (0.19%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 1018 (0.00%)	3 / 1056 (0.28%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Abdominal Pain			
subjects affected / exposed	2 / 1018 (0.20%)	2 / 1056 (0.19%)	3 / 1100 (0.27%)
occurrences causally related to treatment / all	1 / 2	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental Injury			
subjects affected / exposed	0 / 1018 (0.00%)	3 / 1056 (0.28%)	3 / 1100 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Aggravation Reaction			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Allergic Reaction			

subjects affected / exposed	2 / 1018 (0.20%)	5 / 1056 (0.47%)	7 / 1100 (0.64%)
occurrences causally related to treatment / all	1 / 2	4 / 5	5 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	4 / 1018 (0.39%)	6 / 1056 (0.57%)	3 / 1100 (0.27%)
occurrences causally related to treatment / all	4 / 4	7 / 7	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back Pain			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	3 / 1100 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	7 / 1018 (0.69%)	11 / 1056 (1.04%)	7 / 1100 (0.64%)
occurrences causally related to treatment / all	5 / 9	4 / 13	4 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest Pain			
subjects affected / exposed	5 / 1018 (0.49%)	6 / 1056 (0.57%)	7 / 1100 (0.64%)
occurrences causally related to treatment / all	3 / 5	1 / 7	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cyst			
subjects affected / exposed	0 / 1018 (0.00%)	4 / 1056 (0.38%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	85 / 1018 (8.35%)	86 / 1056 (8.14%)	109 / 1100 (9.91%)
occurrences causally related to treatment / all	93 / 94	88 / 93	120 / 124
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	1 / 1018 (0.10%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune System Disorder			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	68 / 1018 (6.68%)	85 / 1056 (8.05%)	85 / 1100 (7.73%)
occurrences causally related to treatment / all	57 / 82	64 / 99	73 / 107
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Injection Site Pain			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucous Membrane Disorder			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Photosensitivity Reaction			

subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation Injury			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reaction Unevaluable			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deafness			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear Pain			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis Media			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular Disorder			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anorexia			

subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	2 / 1018 (0.20%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	2 / 1100 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 1018 (0.00%)	4 / 1056 (0.38%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 1018 (0.10%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhea			
subjects affected / exposed	2 / 1018 (0.20%)	11 / 1056 (1.04%)	10 / 1100 (0.91%)
occurrences causally related to treatment / all	2 / 2	13 / 13	12 / 13
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Dysphagia			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Esophagitis			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 1018 (0.10%)	3 / 1056 (0.28%)	2 / 1100 (0.18%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Hemorrhage			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hematemesis			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Perforation			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melena			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	3 / 1018 (0.29%)	3 / 1056 (0.28%)	7 / 1100 (0.64%)
occurrences causally related to treatment / all	5 / 5	4 / 5	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perforated Stomach Ulcer			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			

subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Hemorrhage			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomach Ulcer			
subjects affected / exposed	0 / 1018 (0.00%)	2 / 1056 (0.19%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	7 / 1018 (0.69%)	1 / 1056 (0.09%)	4 / 1100 (0.36%)
occurrences causally related to treatment / all	7 / 8	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	12 / 1018 (1.18%)	11 / 1056 (1.04%)	16 / 1100 (1.45%)
occurrences causally related to treatment / all	15 / 17	13 / 15	16 / 16
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Apnea			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 1018 (0.00%)	2 / 1056 (0.19%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bronchiectasis			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnea			

subjects affected / exposed	0 / 1018 (0.00%)	3 / 1056 (0.28%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	1 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Disorder			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	2 / 1100 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Edema			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Fibrosis			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 1018 (0.10%)	2 / 1056 (0.19%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 1018 (0.39%)	3 / 1056 (0.28%)	4 / 1100 (0.36%)
occurrences causally related to treatment / all	4 / 5	1 / 3	1 / 5
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	3 / 1100 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis			

subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	2 / 1100 (0.18%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Application Site Reaction			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exfoliative Dermatitis			
subjects affected / exposed	3 / 1018 (0.29%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal Dermatitis			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Maculopapular Rash			
subjects affected / exposed	4 / 1018 (0.39%)	1 / 1056 (0.09%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	4 / 6	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nail Disorder			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			

subjects affected / exposed	0 / 1018 (0.00%)	3 / 1056 (0.28%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Benign Neoplasm			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Breast Neoplasm			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial Carcinoma			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial Disorder			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hematuria			
subjects affected / exposed	0 / 1018 (0.00%)	2 / 1056 (0.19%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney Failure			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Kidney Function Abnormal			

subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menstrual Disorder			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic Nephropathy			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Disorder			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	2 / 1100 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginitis			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Thyroid Disorder			
subjects affected / exposed	1 / 1018 (0.10%)	0 / 1056 (0.00%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 1018 (0.10%)	1 / 1056 (0.09%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arthritis			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bone Pain			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Disorder			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 1018 (0.10%)	1 / 1056 (0.09%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 1018 (0.10%)	5 / 1056 (0.47%)	5 / 1100 (0.45%)
occurrences causally related to treatment / all	1 / 1	5 / 5	5 / 5
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Edema			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enzymatic Abnormality			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalized Edema			

subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycemia			
subjects affected / exposed	1 / 1018 (0.10%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalemia			
subjects affected / exposed	0 / 1018 (0.00%)	2 / 1056 (0.19%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesemia			
subjects affected / exposed	0 / 1018 (0.00%)	3 / 1056 (0.28%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatremia			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolemia			
subjects affected / exposed	0 / 1018 (0.00%)	1 / 1056 (0.09%)	0 / 1100 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Edema			
subjects affected / exposed	1 / 1018 (0.10%)	1 / 1056 (0.09%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sgot Increased			
subjects affected / exposed	0 / 1018 (0.00%)	0 / 1056 (0.00%)	1 / 1100 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Doxorubicin+Cyclophosphamide (AC) Followed by Docetaxel (ACT)	Docetaxel + Carboplatin + Herceptin (TCH)	AC Followed by Docetaxel + Herceptin (ACTH)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1017 / 1018 (99.90%)	1052 / 1056 (99.62%)	1100 / 1100 (100.00%)
Cardiac disorders			
Hypertension			
subjects affected / exposed	40 / 1018 (3.93%)	78 / 1056 (7.39%)	72 / 1100 (6.55%)
occurrences (all)	59	141	124
Left Heart Failure			
subjects affected / exposed	30 / 1018 (2.95%)	31 / 1056 (2.94%)	71 / 1100 (6.45%)
occurrences (all)	42	53	132
Palpitation			
subjects affected / exposed	69 / 1018 (6.78%)	95 / 1056 (9.00%)	94 / 1100 (8.55%)
occurrences (all)	103	164	155
Tachycardia			
subjects affected / exposed	50 / 1018 (4.91%)	67 / 1056 (6.34%)	62 / 1100 (5.64%)
occurrences (all)	79	107	101
Nervous system disorders			
Anxiety			
subjects affected / exposed	86 / 1018 (8.45%)	70 / 1056 (6.63%)	78 / 1100 (7.09%)
occurrences (all)	134	96	136
Depression			
subjects affected / exposed	106 / 1018 (10.41%)	119 / 1056 (11.27%)	139 / 1100 (12.64%)
occurrences (all)	205	199	256
Dizziness			
subjects affected / exposed	112 / 1018 (11.00%)	130 / 1056 (12.31%)	154 / 1100 (14.00%)
occurrences (all)	179	218	226
Dry Mouth			
subjects affected / exposed	87 / 1018 (8.55%)	37 / 1056 (3.50%)	55 / 1100 (5.00%)
occurrences (all)	163	63	87
Emotional Lability			
subjects affected / exposed	56 / 1018 (5.50%)	41 / 1056 (3.88%)	65 / 1100 (5.91%)
occurrences (all)	90	61	110

Insomnia			
subjects affected / exposed	226 / 1018 (22.20%)	252 / 1056 (23.86%)	288 / 1100 (26.18%)
occurrences (all)	494	488	556
Neuropathy			
subjects affected / exposed	514 / 1018 (50.49%)	406 / 1056 (38.45%)	569 / 1100 (51.73%)
occurrences (all)	1294	940	1416
Vasodilatation			
subjects affected / exposed	364 / 1018 (35.76%)	384 / 1056 (36.36%)	416 / 1100 (37.82%)
occurrences (all)	873	958	993
Blood and lymphatic system disorders			
Lymphedema			
subjects affected / exposed	81 / 1018 (7.96%)	107 / 1056 (10.13%)	94 / 1100 (8.55%)
occurrences (all)	125	176	156
General disorders and administration site conditions			
Abdominal Pain			
subjects affected / exposed	179 / 1018 (17.58%)	240 / 1056 (22.73%)	220 / 1100 (20.00%)
occurrences (all)	312	390	370
Allergic Reaction			
subjects affected / exposed	100 / 1018 (9.82%)	153 / 1056 (14.49%)	137 / 1100 (12.45%)
occurrences (all)	139	225	192
Asthenia			
subjects affected / exposed	838 / 1018 (82.32%)	878 / 1056 (83.14%)	925 / 1100 (84.09%)
occurrences (all)	3138	3138	3476
Back Pain			
subjects affected / exposed	82 / 1018 (8.06%)	96 / 1056 (9.09%)	132 / 1100 (12.00%)
occurrences (all)	124	149	205
Chest Pain			
subjects affected / exposed	73 / 1018 (7.17%)	91 / 1056 (8.62%)	103 / 1100 (9.36%)
occurrences (all)	106	149	163
Chills			
subjects affected / exposed	58 / 1018 (5.70%)	78 / 1056 (7.39%)	88 / 1100 (8.00%)
occurrences (all)	81	94	113
Fever			

subjects affected / exposed	162 / 1018 (15.91%)	145 / 1056 (13.73%)	206 / 1100 (18.73%)
occurrences (all)	217	178	282
Headache			
subjects affected / exposed	301 / 1018 (29.57%)	306 / 1056 (28.98%)	323 / 1100 (29.36%)
occurrences (all)	622	566	625
Infection			
subjects affected / exposed	350 / 1018 (34.38%)	327 / 1056 (30.97%)	445 / 1100 (40.45%)
occurrences (all)	694	583	852
Injection Site Reaction			
subjects affected / exposed	66 / 1018 (6.48%)	84 / 1056 (7.95%)	70 / 1100 (6.36%)
occurrences (all)	100	125	108
Pain			
subjects affected / exposed	222 / 1018 (21.81%)	217 / 1056 (20.55%)	268 / 1100 (24.36%)
occurrences (all)	394	368	527
Amblyopia			
subjects affected / exposed	34 / 1018 (3.34%)	55 / 1056 (5.21%)	52 / 1100 (4.73%)
occurrences (all)	62	95	95
Conjunctivitis			
subjects affected / exposed	111 / 1018 (10.90%)	45 / 1056 (4.26%)	122 / 1100 (11.09%)
occurrences (all)	221	69	239
Dry Eyes			
subjects affected / exposed	41 / 1018 (4.03%)	30 / 1056 (2.84%)	56 / 1100 (5.09%)
occurrences (all)	88	54	98
Lacrimation Disorder			
subjects affected / exposed	210 / 1018 (20.63%)	124 / 1056 (11.74%)	264 / 1100 (24.00%)
occurrences (all)	384	246	534
Taste Perversion			
subjects affected / exposed	291 / 1018 (28.59%)	320 / 1056 (30.30%)	312 / 1100 (28.36%)
occurrences (all)	691	738	699
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	230 / 1018 (22.59%)	252 / 1056 (23.86%)	238 / 1100 (21.64%)
occurrences (all)	486	537	527
Constipation			

subjects affected / exposed	383 / 1018 (37.62%)	351 / 1056 (33.24%)	403 / 1100 (36.64%)
occurrences (all)	874	768	913
Diarrhea			
subjects affected / exposed	439 / 1018 (43.12%)	658 / 1056 (62.31%)	555 / 1100 (50.45%)
occurrences (all)	926	1568	1268
Dyspepsia			
subjects affected / exposed	204 / 1018 (20.04%)	263 / 1056 (24.91%)	273 / 1100 (24.82%)
occurrences (all)	398	509	550
Nausea			
subjects affected / exposed	890 / 1018 (87.43%)	863 / 1056 (81.72%)	967 / 1100 (87.91%)
occurrences (all)	3242	2880	3405
Stomatitis			
subjects affected / exposed	660 / 1018 (64.83%)	564 / 1056 (53.41%)	735 / 1100 (66.82%)
occurrences (all)	1847	1252	1959
Vomiting			
subjects affected / exposed	563 / 1018 (55.30%)	428 / 1056 (40.53%)	628 / 1100 (57.09%)
occurrences (all)	1375	892	1412
Respiratory, thoracic and mediastinal disorders			
Cough Increased			
subjects affected / exposed	187 / 1018 (18.37%)	147 / 1056 (13.92%)	205 / 1100 (18.64%)
occurrences (all)	312	218	361
Dyspnea			
subjects affected / exposed	227 / 1018 (22.30%)	229 / 1056 (21.69%)	270 / 1100 (24.55%)
occurrences (all)	408	442	544
Epistaxis			
subjects affected / exposed	60 / 1018 (5.89%)	170 / 1056 (16.10%)	143 / 1100 (13.00%)
occurrences (all)	85	268	219
Pharyngitis			
subjects affected / exposed	74 / 1018 (7.27%)	60 / 1056 (5.68%)	94 / 1100 (8.55%)
occurrences (all)	98	81	135
Rhinitis			
subjects affected / exposed	175 / 1018 (17.19%)	193 / 1056 (18.28%)	277 / 1100 (25.18%)
occurrences (all)	324	347	501

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1003 / 1018 (98.53%)	1018 / 1056 (96.40%)	1083 / 1100 (98.45%)
occurrences (all)	2350	2486	2556
Dry Skin			
subjects affected / exposed	76 / 1018 (7.47%)	61 / 1056 (5.78%)	101 / 1100 (9.18%)
occurrences (all)	148	100	168
Exfoliative Dermatitis			
subjects affected / exposed	87 / 1018 (8.55%)	32 / 1056 (3.03%)	87 / 1100 (7.91%)
occurrences (all)	189	51	175
Maculopapular Rash			
subjects affected / exposed	275 / 1018 (27.01%)	330 / 1056 (31.25%)	354 / 1100 (32.18%)
occurrences (all)	540	644	680
Nail Disorder			
subjects affected / exposed	507 / 1018 (49.80%)	303 / 1056 (28.69%)	484 / 1100 (44.00%)
occurrences (all)	1075	620	1026
Pruritus			
subjects affected / exposed	38 / 1018 (3.73%)	66 / 1056 (6.25%)	50 / 1100 (4.55%)
occurrences (all)	65	103	71
Rash			
subjects affected / exposed	238 / 1018 (23.38%)	313 / 1056 (29.64%)	279 / 1100 (25.36%)
occurrences (all)	357	526	425
Skin Discoloration			
subjects affected / exposed	65 / 1018 (6.39%)	50 / 1056 (4.73%)	67 / 1100 (6.09%)
occurrences (all)	124	83	123
Sweating			
subjects affected / exposed	67 / 1018 (6.58%)	73 / 1056 (6.91%)	67 / 1100 (6.09%)
occurrences (all)	119	118	104
Renal and urinary disorders			
Breast Pain			
subjects affected / exposed	53 / 1018 (5.21%)	62 / 1056 (5.87%)	59 / 1100 (5.36%)
occurrences (all)	80	107	91
Dysuria			
subjects affected / exposed	24 / 1018 (2.36%)	58 / 1056 (5.49%)	51 / 1100 (4.64%)
occurrences (all)	32	73	76
Menstrual Disorder			

subjects affected / exposed	368 / 1018 (36.15%)	384 / 1056 (36.36%)	356 / 1100 (32.36%)
occurrences (all)	827	907	818
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	439 / 1018 (43.12%)	335 / 1056 (31.72%)	515 / 1100 (46.82%)
occurrences (all)	1003	739	1223
Bone Pain			
subjects affected / exposed	187 / 1018 (18.37%)	144 / 1056 (13.64%)	235 / 1100 (21.36%)
occurrences (all)	393	287	475
Myalgia			
subjects affected / exposed	541 / 1018 (53.14%)	415 / 1056 (39.30%)	614 / 1100 (55.82%)
occurrences (all)	1381	944	1493
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	77 / 1018 (7.56%)	79 / 1056 (7.48%)	85 / 1100 (7.73%)
occurrences (all)	213	218	239
Peripheral Edema			
subjects affected / exposed	339 / 1018 (33.30%)	347 / 1056 (32.86%)	405 / 1100 (36.82%)
occurrences (all)	681	708	862
Weight Gain			
subjects affected / exposed	197 / 1018 (19.35%)	254 / 1056 (24.05%)	262 / 1100 (23.82%)
occurrences (all)	425	559	574
Weight Loss			
subjects affected / exposed	81 / 1018 (7.96%)	69 / 1056 (6.53%)	100 / 1100 (9.09%)
occurrences (all)	164	143	236

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2001	This amendment contained the following substantive changes: • Echocardiography was allowed at study entry (in addition to multiple-gated acquisition [MUGA] scans) for confirmation of a subject's left ventricular ejection fraction (LVEF) status. • Echocardiography guidelines and availability of videotapes of echocardiograms were added. • An LVEF evaluation was added at 36 months (ACT and ACTH) and 37.5 months (TCH) to allow for long-term assessment of cardiac function. • Clarifications regarding the dosing of carboplatin and trastuzumab, according to a subject's weight modification, were added.
30 July 2001	This amendment contained the following substantive changes: • The dosing schedule for trastuzumab monotherapy after completion of chemotherapy was modified from administration once a week to administration every 3 weeks based on the results of two studies of the safety, anti-tumor activity, and pharmacokinetics of trastuzumab when administered every 3 weeks to subjects with HER2-positive (by immunohistochemistry or fluorescence in situ hybridization [FISH]) metastatic breast cancer (MBC). • Guidelines for trastuzumab initiation were modified for the ACTH arm. • The trastuzumab post-infusion observation periods were revised. • The optional HER2 extracellular domain (ECD) and cardiac biochemical marker substudies were extended.
10 April 2002	This amendment contained the following substantive changes: • The TCH regimen was modified so that the platinum salt was limited to carboplatin (ie, cisplatin was no longer allowed), based on updated results from the BCIRG 101 and 102 studies. • The instructions describing the administration of trastuzumab and the dose calculation for carboplatin was clarified. • Measurement of the follicle-stimulating hormone to luteinizing hormone ratio to assess menopausal status in subjects <55 years old with a history of hysterectomy without bilateral ovariectomy was no longer required.
17 March 2005	This amendment contained the following substantive changes: • Statistical considerations were revised as follows: − Based on the results of BCIRG 001 study, the assumed DFS rate at 5 years in the ACT arm was changed from 55% to 70%. − The independed data monitoring committee (IDMC) requested interim efficacy analyses when 300, 450, and 650 DFS events had been observed and a main analysis when 900 DFS events had been observed (the initial protocol called for one interim analysis at 654 events and a final analysis at 1308 events). − In order to gain power for the two comparisons of main interest, a "step-down" testing procedure was proposed (instead of three pairwise comparisons). It was also proposed to use the O'Brien-Fleming spending function instead of the Haybittle-Peto. • Following a request from the IDMC, one additional cardiac safety analysis was to be conducted when all subjects had been observed for at least 9 months. • The indication for adjuvant hormonal therapy was modified to allow the use of aromatase inhibitors for postmenopausal subjects who were estrogen receptor (ER)- or progesteron receptor (PR)-positive, as well as for subjects for whom tamoxifen was contraindicated. • In addition, the use of letrozole was allowed for subjects having completed 5 years of tamoxifen therapy. • Based on American Society of Clinical Oncology 2002 follow-up guidelines, hematologic and blood chemistry evaluations and chest X-rays were no longer required during the follow-up period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/21991949

http://www.ncbi.nlm.nih.gov/pubmed/23814044

http://www.ncbi.nlm.nih.gov/pubmed/23420271

http://www.ncbi.nlm.nih.gov/pubmed/21189395

http://www.ncbi.nlm.nih.gov/pubmed/25649019