Clinical trial results:
Ensayo clínico de fase III randomizado, doble ciego, controlado con placebo para evaluar la eficacia y seguridad de pertuzumab +trastuzumab + docetaxel frente a placebo + trastuzumab +docetaxel en pacientes con cáncer de mama metastático HER2-positivo no tratadas previamente.

A Phase III, Randomized, Double-Blind, Placebo Controlled Clinical Trial To Evaluate The Efficacy And Safety Of Pertuzumab + Trastuzumab + Docetaxel Vs. Placebo + Trastuzumab + Docetaxel In Previously Untreated HER2-Positive Metastatic Breast Cancer

Summary

EudraCT number	2007-002997-72
Trial protocol	FI DE GB ES FR IT LV
Global end of trial date	
Results information	
Result version number	v1
This version publication date	14 July 2016
First version publication date	06 August 2015

Trial information

Trial identification	
Sponsor protocol code	WO20698/TOC4129g
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00567190
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com

Notes:

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

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	11 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2011
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

El objetivo principal de este estudio es comparar la supervivencia libre de progresión (SLP) basándose en las evaluaciones del tumor realizadas por un grupo de revisión independiente (IRF), entre las pacientes de los dos grupos de tratamiento siguientes:
placebo + trastuzumab + docetaxel
frente a
pertuzumab + trastuzumab + docetaxel.

The primary objective was to compare progression-free survival (PFS), based on tumor assessments by an independent review facility (IRF), between participants in two treatment arms (placebo + trastuzumab + docetaxel and pertuzumab + trastuzumab + docetaxel).

Protection of trial subjects:

This study was conducted in full conformance with the principles of the Declaration of Helsinki and its subsequent amendments or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the participant. The study adhered to the principles outlined in the Guideline for Good Clinical Practice ICH Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the participant. In other countries where guidelines for good clinical practice existed, the sponsor and the investigators were to strictly ensure adherence to the stated provisions.
For each potential participant, written informed consent was obtained prior to the performance of any study related procedures and after the aims, methods, anticipated benefits, and potential hazards of the study were adequately explained.
The protocol and any accompanying material provided to the participant (such as participant information sheets or descriptions of the study used to obtain informed consent) were approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) before starting the study. Protocol amendments were also approved by IECs/IRBs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Regulatory reason
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 100
Country: Number of subjects enrolled	Canada: 2

Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	China: 13
Country: Number of subjects enrolled	Costa Rica: 6
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Ecuador: 1
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Guatemala: 5
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Japan: 53
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 3
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Philippines: 30
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Russian Federation: 71
Country: Number of subjects enrolled	Singapore: 20
Country: Number of subjects enrolled	Korea, Republic of: 94
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	Thailand: 38
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	United States: 116
Worldwide total number of subjects	808
EEA total number of subjects	232

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)	681
From 65 to 84 years	126
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1196 participants aged at least 18 years with previously-untreated, (in the metastatic setting), Human Epidermal Growth Factor Receptor 2 (HER2) positive metastatic or locally recurrent unresectable breast cancer were screened. An Interactive Voice Response System used to collect screening information and track participant eligibility.

Period 1

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

Arms

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

Arm description:

Participants received pertuzumab 420 milligrams (mg) intravenously (IV) every 3 weeks (q3w) plus trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w plus docetaxel 75 milligrams per square meters of body surface (mg/m^2) IV q3w for at least 6 cycles.

Arm type	Experimental
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab administered as an IV loading dose of 840 mg at Cycle 1 then at a dose of 420 mg at all subsequent cycles until investigator-assessed radiographic or clinical evidence of progressive disease (PD), unacceptable toxicity, or withdrawal of consent.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herclon, Herceptin
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab administered as an IV loading dose of 8 mg/kg in Cycle 1 and at a dose of 6 mg/kg at all subsequent cycles until investigator-assessed radiographic or clinical evidence of PD, unacceptable toxicity, or withdrawal of consent.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere, Docecad, Docefrez
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel administered as an IV dose of 75 mg/m^2 for at least 6 cycles. For participants who tolerated at least one cycle without any significant toxicity, the docetaxel dose was increased to 100 mg/m^2 at the Investigator's discretion. On or prior to Cycle 6, docetaxel was only discontinued for PD or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment was at the discretion of the participant and treating physician.

Arm title	Placebo + Trastuzumab + Docetaxel

Arm description:

Participants received placebo IV q3w plus trastuzumab 6 mg/kg IV q3w plus docetaxel 75 mg/m^2 IV q3w for at least 6 cycles.

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

Dosage and administration details:

The placebo formulation is equivalent to pertuzumab without the active agent. Participants received placebo IV q3w until investigator-assessed radiographic or clinical evidence of PD, unacceptable toxicity, or withdrawal of consent.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herclon, Herceptin
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab administered as an IV loading dose of 8 mg/kg in Cycle 1 and at a dose of 6 mg/kg at all subsequent cycles until investigator-assessed radiographic or clinical evidence of PD, unacceptable toxicity, or withdrawal of consent.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere, Docecad, Docefrez
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel administered as an IV dose of 75 mg/m^2 for at least 6 cycles. For participants who tolerated at least one cycle without any significant toxicity, the docetaxel dose was increased to 100 mg/m^2 at the Investigator's discretion. On or prior to Cycle 6, docetaxel was only discontinued for PD or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment was at the discretion of the participant and treating physician.

Number of subjects in period 1	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel
Started	402	406
Completed	0	0
Not completed	402	406
Withdrew Consent or Lost to Follow-up	42	43
Death	168	221
Alive and on study treatment	67	37
Alive and in survival follow-up	125	105

Baseline characteristics

Reporting groups	
Reporting group title	Pertuzumab + Trastuzumab + Docetaxel
Reporting group description:	
Participants received pertuzumab 420 milligrams (mg) intravenously (IV) every 3 weeks (q3w) plus trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w plus docetaxel 75 milligrams per square meters of body surface (mg/m^2) IV q3w for at least 6 cycles.	
Reporting group title	Placebo + Trastuzumab + Docetaxel
Reporting group description:	
Participants received placebo IV q3w plus trastuzumab 6 mg/kg IV q3w plus docetaxel 75 mg/m^2 IV q3w for at least 6 cycles.	

Reporting group values	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel	Total
Number of subjects	402	406	808
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	53.4	53.5	
standard deviation	± 10.94	± 11.35	-
Gender categorical			
Units: Subjects			
Female	402	404	806
Male	0	2	2

End points

End points reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Docetaxel
Reporting group description:	
Participants received pertuzumab 420 milligrams (mg) intravenously (IV) every 3 weeks (q3w) plus trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w plus docetaxel 75 milligrams per square meters of body surface (mg/m^2) IV q3w for at least 6 cycles.	
Reporting group title	Placebo + Trastuzumab + Docetaxel
Reporting group description:	
Participants received placebo IV q3w plus trastuzumab 6 mg/kg IV q3w plus docetaxel 75 mg/m^2 IV q3w for at least 6 cycles.	

Primary: Progression-free Survival Determined by an Independent Review Facility

End point title	Progression-free Survival Determined by an Independent Review Facility
End point description:	
PFS was defined as the time from randomization to first documented PD using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 or death from any cause (within 18 weeks of last tumor assessment), whichever occurred first. For target lesions, PD was defined as at least a 20 percent (%) increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Target lesions were selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements by imaging techniques or clinically. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, were identified as target lesions.	
End point type	Primary
End point timeframe:	
Baseline to primary data cut-off 13 May 2011 (up to 3 years, 3 months)	

End point values	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402[1]	406[2]		
Units: Months				
median (confidence interval 95%)	18.5 (15 to 23)	12.4 (10 to 13)		

Notes:

[1] - Intent-to-Treat (ITT) Population: all randomized participants are included in the ITT population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Progression-free Survival by IRF
Comparison groups	Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel

Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as the time from randomization to death from any cause.

End point type	Secondary

End point timeframe:

Baseline to the third data cut-off (11 February 2014) at 389 deaths (approximately 43 months after enrollment of last participant)

End point values	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402[3]	406[4]		
Units: Months				
median (confidence interval 95%)	56.5 (49 to 99999)	40.8 (36 to 48)		

Notes:

[3] - ITT Population: 99999=not evaluable more than 50% of participants were censored for this evaluation
[4] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival Determined by the Investigator

End point title	Progression-free Survival Determined by the Investigator

End point description:

PFS was defined as the time from randomization to first documented PD using RECIST v1.0 or death from any cause (within 18 weeks of last tumor assessment), whichever occurred first. For target lesions, PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Target lesions were selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements by imaging techniques or clinically. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, were identified as target lesions.

End point type	Secondary

End point timeframe:

Baseline to the third data cut-off (11 February 2014) at 389 deaths (approximately 43 months after enrollment of last participant)

End point values	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402[5]	406[6]		
Units: Months				
median (confidence interval 95%)	18.7 (17 to 22)	12.4 (10 to 14)		

Notes:

[5] - ITT Population

[6] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Determined by an Independent Review Facility

End point title	Objective Response Determined by an Independent Review Facility

End point description:

A participant had an objective response if they had a complete response (CR) or a partial response (PR) determined on two consecutive occasions greater than or equal to (≥) 4 weeks apart as determined by the investigator using RECIST v1.0. For target lesions, a CR was defined as the disappearance of all target lesions; a PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. For non-target lesions, a CR was defined as the disappearance of all non-target lesions; a PR was defined as the persistence of 1 or more non-target lesions.

End point type	Secondary

End point timeframe:

Baseline to primary data cut-off on 13 May 2011

End point values	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	343[7]	336[8]		
Units: Percentage of Participants				
number (confidence interval 95%)	80.2 (75.6 to 84.3)	69.3 (64.1 to 74.2)		

Notes:

[7] - ITT Population: only particpants with measurable disease at baseline were included in the analysis

[8] - ITT Population: only particpants with measurable disease at baseline were included in the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response Determined by an Independent Review Facility

End point title	Duration of Objective Response Determined by an Independent

	Review Facility

End point description:

Duration of objective response was defined as the time from the initial response to documented PD or death from any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

Baseline to primary data cut-off on 13 May 2011

End point values	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	275[9]	233[10]		
Units: Weeks				
median (confidence interval 95%)	87.6 (71 to 106)	54.1 (46 to 64)		

Notes:

[9] - ITT Population: only participants with an objective response were included in the analysis

[10] - ITT Population: only participants with an objective response were included in the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptom Progression

End point title	Time to Symptom Progression

End point description:

Time to symptom progression was defined as the time from randomization to the first symptom progression as measured by the Functional Assessment of Cancer Therapy-for participants with Breast Cancer (FACT-B) questionnaire with the Trial Outcomes Index-Physical/Functional/Breast (TOI-PFB) subscale. The FACT-B TOI-PFB subscale contains 24 items from 3 subsections of the FACT-B questionnaire: Physical well-being, functional well-being, and additional concerns for breast cancer participants (breast cancer subscale [BCS]). All items in the questionnaire were rated by the patient on a 5-point scale ranging from 0 (“not at all”) to 4 (“very much”). The total score ranged from 0 to 96. A higher score indicates better perceived quality of life. A positive change score from baseline indicates improvement. Symptom progression was defined as a decrease from baseline of 5 points or more.

End point type	Secondary

End point timeframe:

Baseline to primary data cut-off on 13 May 2011

End point values	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	402[11]	404[12]		
Units: Weeks				
median (confidence interval 95%)	18.4 (18 to 27)	18.3 (18 to 27)		

Notes:

[11] - ITT Population: analysis included only female participants

[12] - ITT Population: analysis included only female participants

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First treatment dose (12 February 2008) through final data analysis cut-off (11 February 2014) for a total safety analysis time frame of 6 years. The AE data derived from a snapshot taken on 24 March 2014 of the final analysis dataset (11 February 2014).

Adverse event reporting additional description:

Of those who started the study (pertuzumab [Ptz]=402, placebo[Pla]=406), 2 patients in each group received no treatment (total of 4), 9 Pla patients received at least 1 dose of Ptz, 1 Ptz patient received Pla at every cycle; resulting in Ptz=408 (402-2+9-1) and Pla=396 (406-2-9+1)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Docetaxel

Reporting group description:

Participants received pertuzumab 420 mg IV q3w plus trastuzumab 6 mg/kg IV q3w plus docetaxel 75 mg/m^2 IV q3w for at least 6 cycles.

Reporting group title	Placebo + Trastuzumab + Docetaxel

Reporting group description:

Patients received placebo IV q3w plus trastuzumab 6 mg/kg IV q3w plus docetaxel 75 mg/m^2 IV q3w for at least 6 cycles. For the 48 patients that crossed over to the pertuzumab treatment group, AEs were analyzed from the day of their first placebo dose (Day 1) through the day just prior to their first pertuzumab dose. Any AEs occurring on, or after, the day of their first dose of pertuzumab were included in the Crossover treatment group analysis.

Reporting group title	Crossover From Placebo to Pertuzumab

Reporting group description:

Forty-eight of 406 participants (11.8%) randomized to the placebo treatment group whose disease had not progressed crossed over to an open-label pertuzumab treatment group between July 2012 and November 2012. Participants received pertuzumab administered as an IV loading dose of 840 mg at cycle 1 then 420 mg IV every q3w until investigator-assessed radiographic or clinical evidence of PD, unacceptable toxicity, or withdrawal of consent. Trastuzumab and docetaxel doses continued in accordance with the pre-crossover placebo treatment regimens and according to dosing specifications indicated in the study protocol.

Serious adverse events	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel	Crossover From Placebo to Pertuzumab
Total subjects affected by serious adverse events			
subjects affected / exposed	149 / 408 (36.52%)	116 / 396 (29.29%)	6 / 48 (12.50%)
number of deaths (all causes)	168	220	1
number of deaths resulting from adverse events	8	12	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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

Colon cancer			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Glioblastoma multiforme			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Ocular neoplasm			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Pituitary tumour benign			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Tumour haemorrhage			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Uterine leiomyoma			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 408 (0.74%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	1 / 408 (0.25%)	1 / 396 (0.25%)	0 / 48 (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
Aortic stenosis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Haematoma			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Hypertensive crisis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Hypotension			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Venous thrombosis limb			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 408 (1.47%)	3 / 396 (0.76%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	2 / 6	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 408 (0.25%)	2 / 396 (0.51%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	2 / 408 (0.49%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	2 / 408 (0.49%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 408 (0.00%)	2 / 396 (0.51%)	0 / 48 (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
Influenza like illness			
subjects affected / exposed	2 / 408 (0.49%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	1 / 408 (0.25%)	1 / 396 (0.25%)	0 / 48 (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
Death			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1

Drowning			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	3 / 408 (0.74%)	3 / 396 (0.76%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	3 / 408 (0.74%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	1 / 408 (0.25%)	1 / 396 (0.25%)	0 / 48 (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
Reproductive system and breast disorders			
Breast haemorrhage			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Metrorrhagia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Vaginal haemorrhage			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	2 / 408 (0.49%)	4 / 396 (1.01%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	5 / 408 (1.23%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 408 (0.49%)	2 / 396 (0.51%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	2 / 408 (0.49%)	0 / 396 (0.00%)	0 / 48 (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
Pneumothorax			
subjects affected / exposed	1 / 408 (0.25%)	1 / 396 (0.25%)	0 / 48 (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
Asthma			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Pneumonitis			

subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Respiratory failure			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood electrolytes abnormal			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Blood glucose increased			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Ejection fraction decreased			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	3 / 408 (0.74%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Compression fracture			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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

Contusion			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Fracture			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Post procedural discomfort			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Scapula fracture			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Tendon injury			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Thermal burn			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Tibia fracture			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	6 / 408 (1.47%)	7 / 396 (1.77%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	6 / 6	7 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	0 / 408 (0.00%)	3 / 396 (0.76%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 408 (0.00%)	3 / 396 (0.76%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 3	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Coronary artery disease			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Ventricular fibrillation			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 408 (0.25%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Convulsion			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Monoparesis			

subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Somnolence			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
VIIth nerve paralysis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	46 / 408 (11.27%)	20 / 396 (5.05%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	48 / 48	22 / 23	0 / 0
deaths causally related to treatment / all	3 / 3	1 / 1	0 / 0
Neutropenia			
subjects affected / exposed	18 / 408 (4.41%)	19 / 396 (4.80%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	23 / 23	20 / 20	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			

subjects affected / exposed	3 / 408 (0.74%)	3 / 396 (0.76%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	3 / 4	3 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Granulocytopenia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Leukopenia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	2 / 408 (0.49%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 408 (3.19%)	5 / 396 (1.26%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	12 / 16	3 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 408 (0.49%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 408 (0.00%)	2 / 396 (0.51%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intestinal perforation			
subjects affected / exposed	0 / 408 (0.00%)	2 / 396 (0.51%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Oesophagitis			
subjects affected / exposed	2 / 408 (0.49%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Colitis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Enteritis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Haemorrhoidal haemorrhage			

subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Haemorrhoids			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Intestinal ischaemia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Intestinal obstruction			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Nausea			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Hepatobiliary disorders			
Cholecystitis acute			

subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Cholelithiasis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Hepatic failure			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Drug eruption			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 408 (0.25%)	1 / 396 (0.25%)	0 / 48 (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
Renal failure acute			
subjects affected / exposed	0 / 408 (0.00%)	2 / 396 (0.51%)	0 / 48 (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
Acute prerenal failure			

subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Nephrolithiasis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure chronic			
subjects affected / exposed	0 / 408 (0.00%)	0 / 396 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 408 (0.49%)	1 / 396 (0.25%)	0 / 48 (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
Myalgia			
subjects affected / exposed	1 / 408 (0.25%)	1 / 396 (0.25%)	0 / 48 (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
Mobility decreased			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Muscular weakness			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Neck pain			

subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Osteonecrosis of jaw			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 408 (1.23%)	9 / 396 (2.27%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	2 / 5	2 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Cellulitis			
subjects affected / exposed	10 / 408 (2.45%)	2 / 396 (0.51%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	4 / 10	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic infection			
subjects affected / exposed	4 / 408 (0.98%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	3 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 408 (0.49%)	2 / 396 (0.51%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 408 (0.25%)	3 / 396 (0.76%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	4 / 408 (0.98%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 408 (0.25%)	3 / 396 (0.76%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 408 (0.74%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	2 / 408 (0.49%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 408 (0.00%)	2 / 396 (0.51%)	0 / 48 (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
Erysipelas			
subjects affected / exposed	2 / 408 (0.49%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 408 (0.00%)	2 / 396 (0.51%)	0 / 48 (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
Pharyngitis			
subjects affected / exposed	2 / 408 (0.49%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 408 (0.25%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	1 / 408 (0.25%)	1 / 396 (0.25%)	0 / 48 (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
Upper respiratory tract infection			
subjects affected / exposed	2 / 408 (0.49%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	2 / 408 (0.49%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 408 (0.00%)	2 / 396 (0.51%)	0 / 48 (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
Acute sinusitis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Anal abscess			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cellulitis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Campylobacter gastroenteritis			

subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Catheter site infection			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Coccidioidomycosis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Diarrhoea infectious			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
H1N1 influenza			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Onychomycosis			

subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Oral candidiasis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Osteomyelitis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Osteomyelitis chronic			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Pneumonia staphylococcal			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Postoperative wound infection			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Rash pustular			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Respiratory tract infection viral			

subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Soft tissue infection			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Cellulitis gangrenous			
subjects affected / exposed	0 / 408 (0.00%)	0 / 396 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node tuberculosis			
subjects affected / exposed	0 / 408 (0.00%)	0 / 396 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			

subjects affected / exposed	2 / 408 (0.49%)	1 / 396 (0.25%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 408 (0.25%)	2 / 396 (0.51%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	1 / 1	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Diabetes mellitus			
subjects affected / exposed	0 / 408 (0.00%)	1 / 396 (0.25%)	0 / 48 (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
Fluid retention			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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
Hypoglycaemia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 396 (0.00%)	0 / 48 (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

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

Non-serious adverse events	Pertuzumab + Trastuzumab + Docetaxel	Placebo + Trastuzumab + Docetaxel	Crossover From Placebo to Pertuzumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	400 / 408 (98.04%)	386 / 396 (97.47%)	39 / 48 (81.25%)
Vascular disorders			
Hypertension			
subjects affected / exposed	45 / 408 (11.03%)	32 / 396 (8.08%)	0 / 48 (0.00%)
occurrences (all)	70	94	0
Hot flush			
subjects affected / exposed	23 / 408 (5.64%)	21 / 396 (5.30%)	0 / 48 (0.00%)
occurrences (all)	26	39	0
Lymphoedema			
subjects affected / exposed	24 / 408 (5.88%)	16 / 396 (4.04%)	0 / 48 (0.00%)
occurrences (all)	25	18	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	154 / 408 (37.75%)	148 / 396 (37.37%)	4 / 48 (8.33%)
occurrences (all)	315	290	8
Asthenia			
subjects affected / exposed	112 / 408 (27.45%)	122 / 396 (30.81%)	0 / 48 (0.00%)
occurrences (all)	260	268	0
Oedema peripheral			
subjects affected / exposed	98 / 408 (24.02%)	111 / 396 (28.03%)	0 / 48 (0.00%)
occurrences (all)	134	163	0
Mucosal inflammation			
subjects affected / exposed	111 / 408 (27.21%)	78 / 396 (19.70%)	0 / 48 (0.00%)
occurrences (all)	184	111	0
Pyrexia			
subjects affected / exposed	78 / 408 (19.12%)	72 / 396 (18.18%)	3 / 48 (6.25%)
occurrences (all)	126	94	4
Oedema			
subjects affected / exposed	48 / 408 (11.76%)	49 / 396 (12.37%)	0 / 48 (0.00%)
occurrences (all)	82	76	0
Chills			
subjects affected / exposed	34 / 408 (8.33%)	15 / 396 (3.79%)	0 / 48 (0.00%)
occurrences (all)	36	18	0
Chest pain			

subjects affected / exposed	14 / 408 (3.43%)	21 / 396 (5.30%)	0 / 48 (0.00%)
occurrences (all)	16	24	0
Influenza like illness			
subjects affected / exposed	22 / 408 (5.39%)	9 / 396 (2.27%)	0 / 48 (0.00%)
occurrences (all)	39	11	0
Pain			
subjects affected / exposed	26 / 408 (6.37%)	22 / 396 (5.56%)	0 / 48 (0.00%)
occurrences (all)	30	27	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	26 / 408 (6.37%)	21 / 396 (5.30%)	0 / 48 (0.00%)
occurrences (all)	31	29	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	96 / 408 (23.53%)	79 / 396 (19.95%)	3 / 48 (6.25%)
occurrences (all)	135	117	4
Dyspnoea			
subjects affected / exposed	61 / 408 (14.95%)	62 / 396 (15.66%)	0 / 48 (0.00%)
occurrences (all)	91	87	0
Epistaxis			
subjects affected / exposed	41 / 408 (10.05%)	35 / 396 (8.84%)	0 / 48 (0.00%)
occurrences (all)	55	47	0
Oropharyngeal pain			
subjects affected / exposed	32 / 408 (7.84%)	27 / 396 (6.82%)	0 / 48 (0.00%)
occurrences (all)	51	32	0
Rhinorrhoea			
subjects affected / exposed	32 / 408 (7.84%)	23 / 396 (5.81%)	0 / 48 (0.00%)
occurrences (all)	41	29	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	64 / 408 (15.69%)	55 / 396 (13.89%)	0 / 48 (0.00%)
occurrences (all)	86	72	0
Depression			
subjects affected / exposed	26 / 408 (6.37%)	20 / 396 (5.05%)	0 / 48 (0.00%)
occurrences (all)	32	23	0
Anxiety			

subjects affected / exposed	16 / 408 (3.92%)	20 / 396 (5.05%)	0 / 48 (0.00%)
occurrences (all)	21	28	0
Investigations			
Weight decreased			
subjects affected / exposed	36 / 408 (8.82%)	19 / 396 (4.80%)	0 / 48 (0.00%)
occurrences (all)	50	22	0
Weight increased			
subjects affected / exposed	16 / 408 (3.92%)	22 / 396 (5.56%)	0 / 48 (0.00%)
occurrences (all)	20	35	0
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	22 / 408 (5.39%)	27 / 396 (6.82%)	0 / 48 (0.00%)
occurrences (all)	32	33	0
Nervous system disorders			
Headache			
subjects affected / exposed	105 / 408 (25.74%)	76 / 396 (19.19%)	6 / 48 (12.50%)
occurrences (all)	175	127	8
Neuropathy peripheral			
subjects affected / exposed	91 / 408 (22.30%)	79 / 396 (19.95%)	0 / 48 (0.00%)
occurrences (all)	131	114	0
Dysgeusia			
subjects affected / exposed	75 / 408 (18.38%)	62 / 396 (15.66%)	0 / 48 (0.00%)
occurrences (all)	95	116	0
Dizziness			
subjects affected / exposed	61 / 408 (14.95%)	53 / 396 (13.38%)	0 / 48 (0.00%)
occurrences (all)	123	73	0
Peripheral sensory neuropathy			
subjects affected / exposed	50 / 408 (12.25%)	59 / 396 (14.90%)	0 / 48 (0.00%)
occurrences (all)	90	82	0
Paraesthesia			
subjects affected / exposed	40 / 408 (9.80%)	41 / 396 (10.35%)	0 / 48 (0.00%)
occurrences (all)	49	60	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	209 / 408 (51.23%)	191 / 396 (48.23%)	0 / 48 (0.00%)
occurrences (all)	848	797	0
Anaemia			

subjects affected / exposed	96 / 408 (23.53%)	77 / 396 (19.44%)	5 / 48 (10.42%)
occurrences (all)	141	143	7
Leukopenia			
subjects affected / exposed	75 / 408 (18.38%)	82 / 396 (20.71%)	0 / 48 (0.00%)
occurrences (all)	288	344	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	60 / 408 (14.71%)	55 / 396 (13.89%)	0 / 48 (0.00%)
occurrences (all)	72	63	0
Conjunctivitis			
subjects affected / exposed	31 / 408 (7.60%)	17 / 396 (4.29%)	0 / 48 (0.00%)
occurrences (all)	41	20	0
Dry eye			
subjects affected / exposed	23 / 408 (5.64%)	8 / 396 (2.02%)	0 / 48 (0.00%)
occurrences (all)	26	8	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	277 / 408 (67.89%)	193 / 396 (48.74%)	22 / 48 (45.83%)
occurrences (all)	949	431	95
Nausea			
subjects affected / exposed	183 / 408 (44.85%)	168 / 396 (42.42%)	4 / 48 (8.33%)
occurrences (all)	388	359	4
Vomiting			
subjects affected / exposed	105 / 408 (25.74%)	96 / 396 (24.24%)	5 / 48 (10.42%)
occurrences (all)	176	150	5
Constipation			
subjects affected / exposed	65 / 408 (15.93%)	100 / 396 (25.25%)	0 / 48 (0.00%)
occurrences (all)	130	179	0
Stomatitis			
subjects affected / exposed	81 / 408 (19.85%)	63 / 396 (15.91%)	3 / 48 (6.25%)
occurrences (all)	153	138	3
Abdominal pain			
subjects affected / exposed	62 / 408 (15.20%)	48 / 396 (12.12%)	0 / 48 (0.00%)
occurrences (all)	84	64	0
Dyspepsia			

subjects affected / exposed	54 / 408 (13.24%)	48 / 396 (12.12%)	3 / 48 (6.25%)
occurrences (all)	77	72	6
Abdominal pain upper			
subjects affected / exposed	43 / 408 (10.54%)	43 / 396 (10.86%)	0 / 48 (0.00%)
occurrences (all)	68	54	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	248 / 408 (60.78%)	240 / 396 (60.61%)	0 / 48 (0.00%)
occurrences (all)	264	256	0
Rash			
subjects affected / exposed	153 / 408 (37.50%)	95 / 396 (23.99%)	8 / 48 (16.67%)
occurrences (all)	273	184	13
Nail disorder			
subjects affected / exposed	96 / 408 (23.53%)	92 / 396 (23.23%)	0 / 48 (0.00%)
occurrences (all)	103	105	0
Pruritus			
subjects affected / exposed	72 / 408 (17.65%)	40 / 396 (10.10%)	0 / 48 (0.00%)
occurrences (all)	110	67	0
Dry skin			
subjects affected / exposed	46 / 408 (11.27%)	24 / 396 (6.06%)	3 / 48 (6.25%)
occurrences (all)	52	25	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	28 / 408 (6.86%)	22 / 396 (5.56%)	0 / 48 (0.00%)
occurrences (all)	38	25	0
Erythema			
subjects affected / exposed	24 / 408 (5.88%)	20 / 396 (5.05%)	0 / 48 (0.00%)
occurrences (all)	29	27	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	23 / 408 (5.64%)	11 / 396 (2.78%)	0 / 48 (0.00%)
occurrences (all)	27	12	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	98 / 408 (24.02%)	98 / 396 (24.75%)	0 / 48 (0.00%)
occurrences (all)	200	209	0
Arthralgia			

subjects affected / exposed	79 / 408 (19.36%)	69 / 396 (17.42%)	3 / 48 (6.25%)
occurrences (all)	123	121	3
Pain in extremity			
subjects affected / exposed	73 / 408 (17.89%)	53 / 396 (13.38%)	0 / 48 (0.00%)
occurrences (all)	107	80	0
Back pain			
subjects affected / exposed	65 / 408 (15.93%)	48 / 396 (12.12%)	3 / 48 (6.25%)
occurrences (all)	86	58	7
Musculoskeletal pain			
subjects affected / exposed	38 / 408 (9.31%)	38 / 396 (9.60%)	0 / 48 (0.00%)
occurrences (all)	45	64	0
Bone pain			
subjects affected / exposed	37 / 408 (9.07%)	34 / 396 (8.59%)	0 / 48 (0.00%)
occurrences (all)	47	59	0
Muscle spasms			
subjects affected / exposed	42 / 408 (10.29%)	20 / 396 (5.05%)	0 / 48 (0.00%)
occurrences (all)	73	24	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	85 / 408 (20.83%)	57 / 396 (14.39%)	5 / 48 (10.42%)
occurrences (all)	150	93	8
Nasopharyngitis			
subjects affected / exposed	69 / 408 (16.91%)	59 / 396 (14.90%)	11 / 48 (22.92%)
occurrences (all)	118	103	25
Urinary tract infection			
subjects affected / exposed	36 / 408 (8.82%)	29 / 396 (7.32%)	0 / 48 (0.00%)
occurrences (all)	53	39	0
Influenza			
subjects affected / exposed	26 / 408 (6.37%)	22 / 396 (5.56%)	4 / 48 (8.33%)
occurrences (all)	37	33	4
Paronychia			
subjects affected / exposed	31 / 408 (7.60%)	16 / 396 (4.04%)	0 / 48 (0.00%)
occurrences (all)	42	23	0
Rhinitis			
subjects affected / exposed	20 / 408 (4.90%)	22 / 396 (5.56%)	3 / 48 (6.25%)
occurrences (all)	45	35	11

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	120 / 408 (29.41%)	106 / 396 (26.77%)	0 / 48 (0.00%)
occurrences (all)	228	176	0
Hypokalaemia			
subjects affected / exposed	37 / 408 (9.07%)	21 / 396 (5.30%)	0 / 48 (0.00%)
occurrences (all)	59	28	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2007	AMENDMENT A Key Elements: - Increased the study sample size from 600 participants to 800 participants - Added participant exclusion criterion for a history of systemic breast cancer treatment - Revised the cardiac safety monitoring plan - Revised the Docetaxel dose adjustments to be at the discretion of the treating physician based on tolerability - Added a substudy allowing for an evaluation of the corrected QT Interval (QTc) prolongation based on tolerability at selected sites - Added assessment for anti-therapeutic antibodies (ATA) to pertuzumab - Revised the definition of the primary endpoint of PFS - Defined the censoring of PFS data - Revised the collection of radiographic tumor assessment data until IRF confirmed PD - Changed the interim and final analysis timelines for OS - Removed clinical benefit rate from the secondary endpoints - Added an Interim safety analysis occurring when 100 participants enrolled and followed for at least four months - Implemented block randomization with two stratification factors instead of the dynamic randomization
12 December 2007	AMENDMENT B key elements: - Modified inclusion criterion 4 to include the collection of historic left ventricular ejection fraction (LVEF) values - Added LVEF assessments during follow-up to allow long-term follow-up of cardiac function - Aligned the reporting and grading of symptomatic left ventricular dysfunction (LVSD) with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0 - Increased surveillance of anti-pertuzumab antibodies - Updated statistical analysis plan in relation to objective response, and statistical considerations and the analytical plan were further clarified - Added a hematology test on Day 8 of each treatment cycle during chemotherapy - Described with more accuracy the tumor assessment scans required at baseline

23 June 2009	AMENDMENT C key elements: - Updated definition of postmenopausal women and the contraceptive requirements for women of childbearing potential, male participants with partners of childbearing potential, and pregnant partners to align with Medicines and Health Care Products Regulatory Agency (MHRA) recommendations, in accordance with the International Conference on Harmonization (ICH) M3 guideline - Added pregnancy testing requirements after discontinuation of study treatment - Clarified eligibility for enrollment into the study for participants with bone-only metastases - Clarified prior hormonal therapy in the metastatic breast cancer (MBC) setting and exclusion criterion 6 was amended to allow enrollment of participants with a history of squamous cell carcinoma - Clarified non-eligibility for participants in other interventional and non-interventional studies - Added clarification to exclusion criterion 14 regarding acceptable transaminases and alkaline phosphatase levels for inclusion into the study - Updated the schedule of assessments, deleting unnecessary assessments and correcting time points at which an assessment was required - Clarified use of positron emission tomography/computed tomography (PET/CT) scans when bone scans could not performed due to isotope shortages - Clarified the administration and discontinuation of docetaxel - Clarified the follow-up period for LVEF assessments following discontinuation of study treatment
26 August 2011	AMENDMENT D key elements: - Continuation of tumor assessments until investigator-determined PD (instead of IRF-determined PD) or until 15 April 2012 (with the exception of sites in Japan) - Continuation of sites in Japan to perform tumor assessments until IRF-determined disease progression and send tumor assessment data to the IRF until notified by the Study Management Team - Maintained the study blinding procedures to reduce the chances of bias or crossover occurring after disease progression - Updated timelines for the quality-of-life assessment (FACT-B questionnaire), sampling for antibodies to pertuzumab, and Eastern Cooperative Oncology Group (ECOG) performance status assessments - Eliminated sampling for shed HER2 extracellular domain (ECD) and HER ligands
04 May 2012	AMENDMENT E key elements: - Inserted information relating to the second interim OS analysis as requested by regulatory authorities - Added an open-label pertuzumab crossover treatment group offered to participants in the placebo treatment group who had not experienced disease progression and were still receiving study treatment. The addition of the open-label pertuzumab crossover treatment group was subject to the results of the second interim OS analysis and was allowed because a statistical significance was achieved at the second interim OS analysis. - Added a change in serious adverse event (SAE) reporting that all SAEs should be reported to the Sponsor within 24 hours of the investigator becoming aware of the event to comply with European regulations

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported