Clinical trial results:
A randomised, multicentre, multinational Phase II study to evaluate pertuzumab in combination with trastuzumab given either concomitantly or sequentially with standard anthracycline based chemotherapy or concomitantly with a non-anthracycline based chemotherapy regimen, as neoadjuvant therapy for subjects with locally advanced, inflammatory or early stage HER2-positive breast cancer.

Summary

EudraCT number	2009-012019-17
Trial protocol	IT DE GB PT GR SE
Global end of trial date	25 January 2016

Results information

Result version number	v2 (current)
This version publication date	09 February 2017
First version publication date	26 June 2015
Version creation reason	• New data added to full data set Final results data are added to existing primary analysis data.

Trial information

Trial identification

Sponsor protocol code	BO22280

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00976989
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To make a preliminary assessment of the tolerability of neoadjuvant treatment with one of the following treatment regimens: Sequential chemotherapy, consisting of cycles of a standard therapy for breast cancer consisting of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) chemotherapy followed by cycles of docetaxel (FEC->T) with trastuzumab and pertuzumab given from the start of the chemotherapy regimen (i.e. concurrently with the anthracycline). (Arm A). OR FEC ->T with trastuzumab and pertuzumab given from the start of the taxane treatment (i.e. sequentially with the anthracycline). (Arm B). OR Trastuzumab, carboplatin, docetaxel (TCH) with pertuzumab, with both antibodies being given from the start of the chemotherapy. (Arm C).

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 November 2009
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	Switzerland: 13
Country: Number of subjects enrolled	Bahamas: 1
Country: Number of subjects enrolled	Bosnia and Herzegovina: 9
Country: Number of subjects enrolled	Brazil: 33
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	China: 17
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Spain: 26

Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Italy: 11
Worldwide total number of subjects	225
EEA total number of subjects	105

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)	199
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study included 3 periods: Neoadjuvant (pre-operative) period and surgery, adjuvant (post-operative) period and post-treatment follow-up period.

Pre-assignment

Screening details:

A total of 300 subjects with early stage HER2-positive breast cancer were screened, of whom 225 were randomised.

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	T+P Concomitant Anthracycline-based Chemotherapy

Arm description:

5-Fluorouracil, epirubicin with cyclophosphamide (FEC), trastuzumab and pertuzumab every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 17 as adjuvant therapy post-surgery.

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

Dosage and administration details:

Trastuzumab was given as an IV infusion, at a loading dose of 8 mg/kg. Three weeks (21 days) after the first dose, and every three weeks thereafter, an IV dose of 6 mg/kg was given.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-Fluorouracil was administered in accordance with the local prescribing information; 500 mg/m^2.

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

Dosage and administration details:

Epirubicin was administered in accordance with the local prescribing information; 100 mg/m^2.

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

Dosage and administration details:

Cyclophosphamide was administered in accordance with the local prescribing information; 600 mg/m^2.

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

Dosage and administration details:

Pertuzumab was given as an IV infusion at a loading dose of 840 mg. Three weeks (21 days) after the first dose, and every three weeks thereafter, an IV dose of 420 mg pertuzumab was given.

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

Dosage and administration details:

Docetaxel was administered in accordance with the local prescribing information; 75 mg/m^2 for the first dose; 100 mg/m^2 if no dose limiting toxicity occurs.

Arm title	T+P Sequential Anthracycline-based Chemotherapy

Arm description:

FEC every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 21 as adjuvant therapy post-surgery.

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

Dosage and administration details:

Trastuzumab was given as an IV infusion, at a loading dose of 8 mg/kg. Three weeks (21 days) after the first dose, and every three weeks thereafter, an IV dose of 6 mg/kg was given.

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

Dosage and administration details:

Pertuzumab was given as an IV infusion at a loading dose of 840 mg. Three weeks (21 days) after the first dose, and every three weeks thereafter, an IV dose of 420 mg pertuzumab was given.

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

Dosage and administration details:

Docetaxel was administered in accordance with the local prescribing information; 75 mg/m^2 for the first dose; 100 mg/m^2 if no dose limiting toxicity occurs.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

5-Fluorouracil was administered in accordance with the local prescribing information; 500 mg/m^2.

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

Dosage and administration details:

Epirubicin was administered in accordance with the local prescribing information; 100 mg/m^2.

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

Dosage and administration details:

Cyclophosphamide was administered in accordance with the local prescribing information: 600 mg/m^2.

Arm title	T+P Concomitant Non-Anthracycline Chemotherapy

Arm description:

Trastuzumab, carboplatin, docetaxel (TCH) and pertuzumab every three weeks, for six cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 17 as adjuvant therapy post-surgery.

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

Dosage and administration details:

Trastuzumab was given as an IV infusion, at a loading dose of 8 mg/kg. Three weeks (21 days) after the first dose, and every three weeks thereafter, an IV dose of 6 mg/kg was given.

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

Dosage and administration details:

Docetaxel was administered in accordance with the local prescribing information; 75 mg/m^2 for the first dose; 100 mg/m^2 if no dose limiting toxicity occurs.

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

Dosage and administration details:

Carboplatin was administered in accordance with the local prescribing information; at target area under the plasma concentration-time curve (AUC) 6.

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

Dosage and administration details:

Pertuzumab was given as an IV infusion at a loading dose of 840 mg. Three weeks (21 days) after the first dose, and every three weeks thereafter, an IV dose of 420 mg pertuzumab was given.

Number of subjects in period 1	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy
Started	73	75	77
Completed	60	63	60
Not completed	13	12	17
Refused Treatment	4	3	5
Death	5	7	10
Recurrence of Disease	-	1	-
Unspecified	1	-	1
Failure to Return	2	1	-
Violation of Selection Criteria at Entry	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	T+P Concomitant Anthracycline-based Chemotherapy
Reporting group description:	
5-Fluorouracil, epirubicin with cyclophosphamide (FEC), trastuzumab and pertuzumab every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 17 as adjuvant therapy post-surgery.	
Reporting group title	T+P Sequential Anthracycline-based Chemotherapy
Reporting group description:	
FEC every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 21 as adjuvant therapy post-surgery.	
Reporting group title	T+P Concomitant Non-Anthracycline Chemotherapy
Reporting group description:	
Trastuzumab, carboplatin, docetaxel (TCH) and pertuzumab every three weeks, for six cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 17 as adjuvant therapy post-surgery.	

Reporting group values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy
Number of subjects	73	75	77
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	49.6	50.5	50.6
standard deviation	± 11.41	± 10.7	± 10.58
Gender categorical			
Units: Subjects			
Female	73	75	77
Male	0	0	0

Reporting group values	Total		
Number of subjects	225		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	225		
Male	0		

End points

End points reporting groups

Reporting group title	T+P Concomitant Anthracycline-based Chemotherapy

Reporting group description:

5-Fluorouracil, epirubicin with cyclophosphamide (FEC), trastuzumab and pertuzumab every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 17 as adjuvant therapy post-surgery.

Reporting group title	T+P Sequential Anthracycline-based Chemotherapy

Reporting group description:

FEC every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 21 as adjuvant therapy post-surgery.

Reporting group title	T+P Concomitant Non-Anthracycline Chemotherapy

Reporting group description:

Trastuzumab, carboplatin, docetaxel (TCH) and pertuzumab every three weeks, for six cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 17 as adjuvant therapy post-surgery.

Primary: Percentage of Subjects With Symptomatic Cardiac Events as Assessed by the Investigator

End point title	Percentage of Subjects With Symptomatic Cardiac Events as Assessed by the Investigator[1]

End point description:

Left ventricular systolic dysfunction (LVSD) as assessed by the Investigator, including Grade 3, 4 or 5 symptomatic LVSD with symptomatic cardiac events. Safety population included all subjects who were randomised and received study drug.

End point type	Primary

End point timeframe:

From baseline up to approximately 3.5 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 analysis was planned for this endpoint.

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	75	76	
Units: percentage of subjects				
number (not applicable)	0	2.7	1.3	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Left Ventricular Ejection Fraction (LVEF) Decline During Pre-operative (Neoadjuvant) Period

End point title	Percentage of Subjects With Left Ventricular Ejection Fraction (LVEF) Decline During Pre-operative (Neoadjuvant) Period[2]

End point description:

Percentage of subjects with LVEF measures decline of ≥ 10% from baseline and to a value of <50% during the pre-operative (neoadjuvant) period. Safety population included all subjects who were randomised and received study drug.

End point type	Primary

End point timeframe:

From baseline up to approximately 18 weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned for this endpoint.

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	75	76	
Units: percentage of subjects				
number (not applicable)	5.6	5.3	3.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Complete Pathological Response (pCR)

End point title	Percentage of Subjects With Complete Pathological Response (pCR)

End point description:

pCR is defined as the absence of invasive neoplastic cells at microscopic examination of the tumour remnants after surgery following primary systemic therapy. pCR is evaluated after 6 cycles of treatment and surgery or following withdrawal from the study whichever occurs sooner. Intent to treat (ITT) population included all subjects who were randomised to treatment.

End point type	Secondary

End point timeframe:

At surgery, after 18 weeks (6 cycles) of treatment

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	75	77	
Units: percentage of subjects				
number (confidence interval 95%)	61.6 (49.5 to	57.3 (45.4 to	66.2 (54.6 to	

72.8)	68.7)	76.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Response Rate

End point title	Clinical Response Rate

End point description:

Tumour response is defined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) and is identified as per local practice. Clinical response rate is defined as the percentage of subjects who achieve a response of CR or PR at any time pre-surgery. Per Response Evaluation Criteria in Solid Tumours Criteria (RECIST v1.0) for target lesions and assessed by mammogram or magnetic resonance imaging (MRI) and clinical breast examination (CBE): CR is disappearance of all target lesions; PR is >=30% decrease in the sum of the longest diameter of target lesions.

End point type	Secondary

End point timeframe:

During each 3-week cycle of 6 total cycles: up to 18 weeks

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	75	77	
Units: percentage of subjects				
number (not applicable)	91.8	94.7	89.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Clinical Response

End point title	Time to Clinical Response

End point description:

Time to clinical response rate is defined as the time from the date of first dose received to the first date of assessment of clinical response. Clinical response is defined as a response of CR or PR at any time pre-surgery. Per RECIST v1.0 for target lesions and assessed by mammogram or MRI and CBE, CR is disappearance of all target lesions; PR is >=30% decrease in the sum of the longest diameter of target lesions. ITT population included all subjects who were randomised to treatment.

End point type	Secondary

End point timeframe:

Up to 18 weeks

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	75	77	
Units: weeks				
median (confidence interval 95%)	3.6 (3 to 6)	6.3 (6 to 7)	4.9 (4 to 6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving Breast Conserving Surgery

End point title	Percentage of Subjects Achieving Breast Conserving Surgery

End point description:

This is the percentage of subjects who achieved breast conserving surgery out of the intent-to-treat population without inflammatory breast cancer, as these subjects received mastectomy irrespective of their response to neoadjuvant (pre-operative) treatment. Number of subjects analysed represents the subjects with T2-3 tumours for whom mastectomy was planned.

End point type	Secondary

End point timeframe:

At approximately 18 weeks

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	36	37	
Units: percentage of subjects				
number (not applicable)	21.7	16.7	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Without an Overall Survival (OS) Event

End point title	Percentage of Subjects Without an Overall Survival (OS) Event

End point description:

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

Subjects who were alive or lost to follow-up were censored at the last known alive date. Subjects with no post-baseline information were censored. ITT population included all subjects who were randomised to treatment.

End point type	Secondary

End point timeframe:

From baseline to end of study up to 5 years

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	75	77	
Units: percentage of subjects				
number (not applicable)	93.2	90.7	87	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Without a Disease-Free Survival (DFS) Event

End point title	Percentage of Subjects Without a Disease-Free Survival (DFS) Event

End point description:

The DFS was defined as the time from the first date of no disease (i.e., date of surgery) to the first documentation of progressive disease (PD) or death. PD was assessed using RECIST v1.0 and mammogram or MRI and CBE. It was defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Any evidence of contralateral disease in situ was not considered as PD. Subjects who were withdrawn from the study without documented PD were censored at the date of the last assessment when the subject was known to be disease-free. ITT population included all subjects who were randomised to treatment. Number of subjects analysed is total number of subjects evaluable during each period.

End point type	Secondary

End point timeframe:

From baseline to end of study up to 5 years

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	67	72	
Units: percentage of subjects				
number (not applicable)	85.5	88.1	84.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Without a Progression-Free Survival (PFS) Event

End point title	Percentage of Subjects Without a Progression-Free Survival (PFS) Event

End point description:

Progression-free survival was defined as the time from the date of randomisation to the first documentation of PD or death from any cause, whichever occurred first. PD was assessed using RECIST v1.0 and mammogram or MRI and CBE. It was defined as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Subjects who were withdrawn from the study without documented PD were censored at the date of the last assessment when the subject was known to be free from PD. Subjects without post-baseline assessments but known to be alive were censored at the time of randomisation plus one day. ITT population included all subjects who were randomised to treatment.

End point type	Secondary

End point timeframe:

From baseline to end of study up to 5 years

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	75	77	
Units: percentage of subjects				
number (not applicable)	86.3	85.3	81.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Cardiac Symptoms Associated With Symptomatic Left Ventricular Systolic Dysfunction (LVSD)

End point title	Percentage of Subjects With Cardiac Symptoms Associated With Symptomatic Left Ventricular Systolic Dysfunction (LVSD)

End point description:

Percentage of subjects with signs or symptoms of cardiac events. Safety analysis population included all randomised subjects who received treatment. Number of subjects analysed is total number of subjects evaluable during each period.

End point type	Secondary

End point timeframe:

From Baseline to end of Neoadjuvant Period (up to 18 weeks), Adjuvant Period (up to 1.5 years), Follow-up Period (up to 3.5 years)

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	75	76	
Units: percentage of subjects				
number (not applicable)				
Neoadjuvant Period (n=72, 75, 76)	1.4	2.7	0	
Adjuvant Period (n= 68, 65, 67)	0	0	1.5	
Follow-up Period (n=70, 75, 74)	0	1.3	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Asymptomatic Left Ventricular Ejection Fraction (LVEF) Events

End point title	Percentage of Subjects With Asymptomatic Left Ventricular Ejection Fraction (LVEF) Events

End point description:

Percentage of subjects with LVEF events without signs or symptoms of cardiac events. Safety analysis population included all randomised subjects who received treatment. Number of subjects analysed is total number of subjects evaluable during each period.

End point type	Secondary

End point timeframe:

From baseline to end of Neoadjuvant Period (up to 18 weeks), Adjuvant Period (up to 1.5 years), Follow-up Period (up to 3.5 years)

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	75	76	
Units: percentage of subjects				
number (not applicable)				
Neoadjuvant Period (n=72, 75, 76)	5.6	4	2.6	
Adjuvant Period (n= 66, 64, 63)	3	0	4.8	
Follow-up Period (n=21, 18, 23)	0	11.1	4.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Decrease in Left Ventricular Ejection Fraction (LVEF) Measures

End point title	Maximum Decrease in Left Ventricular Ejection Fraction (LVEF) Measures

End point description:

Maximum decrease in LVEF measures is the change from baseline at worst treatment value. LVEF is measured as percentage. Safety analysis population included all randomised subjects who received treatment. Number of subjects analysed is total number of subjects evaluable.

End point type	Secondary

End point timeframe:

From baseline up to approximately 3.5 years

End point values	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	72	73	
Units: percentage (ejection fraction)				
arithmetic mean (standard deviation)	-6.6 (± 5.15)	-8.4 (± 5.66)	-7 (± 6.48)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 5 years	
Adverse event reporting additional description:	
Safety population included all subjects who were randomised and received study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	T+P Concomitant Anthracycline-based Chemotherapy
Reporting group description:	
5-Fluorouracil, epirubicin with cyclophosphamide (FEC), trastuzumab and pertuzumab every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 17 as adjuvant therapy post-surgery.	
Reporting group title	T+P Sequential Anthracycline-based Chemotherapy
Reporting group description:	
FEC every three weeks for three cycles, followed by docetaxel, trastuzumab and pertuzumab every three weeks, for three cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 21 as adjuvant therapy post-surgery.	
Reporting group title	T+P Concomitant Non-Anthracycline Chemotherapy
Reporting group description:	
Trastuzumab, carboplatin, docetaxel (TCH) and pertuzumab every three weeks, for six cycles as neoadjuvant therapy. Trastuzumab every three weeks from Cycle 7 up to Cycle 17 as adjuvant therapy post-surgery.	

Serious adverse events	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 72 (31.94%)	18 / 75 (24.00%)	31 / 76 (40.79%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic neoplasm			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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
General disorders and administration site conditions			
Mucosal inflammation			

subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	1 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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 necrosis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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

Ovarian cyst			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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
Vaginal haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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			
Epistaxis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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
Pulmonary embolism			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			

subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	1 / 72 (1.39%)	3 / 75 (4.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	1 / 1	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular disorder			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conduction disorder			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
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			
Cerebrovascular accident			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	10 / 72 (13.89%)	4 / 75 (5.33%)	11 / 76 (14.47%)
occurrences causally related to treatment / all	10 / 10	4 / 4	13 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 72 (2.78%)	3 / 75 (4.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	2 / 2	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Leukopenia			
subjects affected / exposed	2 / 72 (2.78%)	0 / 75 (0.00%)	0 / 76 (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
Thrombocytopenia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 72 (1.39%)	3 / 75 (4.00%)	4 / 76 (5.26%)
occurrences causally related to treatment / all	1 / 1	3 / 3	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 72 (0.00%)	2 / 75 (2.67%)	0 / 76 (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
Nausea			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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	2 / 72 (2.78%)	0 / 75 (0.00%)	2 / 76 (2.63%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic infection			
subjects affected / exposed	0 / 72 (0.00%)	2 / 75 (2.67%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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
Appendicitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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
Catheter site infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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
Cystitis			

subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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
Device related infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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
Device related sepsis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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
Gastroenteritis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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
Infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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
Lung Abscess			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomembranous colitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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
Pyelonephritis			

subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
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 infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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
Infectious pleural effusion			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	0 / 76 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	0 / 76 (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

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

Non-serious adverse events	T+P Concomitant Anthracycline-based Chemotherapy	T+P Sequential Anthracycline-based Chemotherapy	T+P Concomitant Non-Anthracycline Chemotherapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 72 (100.00%)	73 / 75 (97.33%)	76 / 76 (100.00%)
Vascular disorders			
Hot Flush			
subjects affected / exposed	11 / 72 (15.28%)	9 / 75 (12.00%)	10 / 76 (13.16%)
occurrences (all)	12	12	12
Hypertension			
subjects affected / exposed	5 / 72 (6.94%)	2 / 75 (2.67%)	5 / 76 (6.58%)
occurrences (all)	5	2	5
Lymphoedema			
subjects affected / exposed	2 / 72 (2.78%)	5 / 75 (6.67%)	4 / 76 (5.26%)
occurrences (all)	2	5	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	30 / 72 (41.67%)	28 / 75 (37.33%)	33 / 76 (43.42%)
occurrences (all)	51	46	46
Mucosal inflammation			
subjects affected / exposed	17 / 72 (23.61%)	15 / 75 (20.00%)	12 / 76 (15.79%)
occurrences (all)	31	21	21
Pyrexia			
subjects affected / exposed	11 / 72 (15.28%)	9 / 75 (12.00%)	15 / 76 (19.74%)
occurrences (all)	11	13	20
Asthenia			
subjects affected / exposed	9 / 72 (12.50%)	14 / 75 (18.67%)	10 / 76 (13.16%)
occurrences (all)	13	24	28
Oedema peripheral			
subjects affected / exposed	10 / 72 (13.89%)	5 / 75 (6.67%)	9 / 76 (11.84%)
occurrences (all)	13	5	11
Pain			
subjects affected / exposed	3 / 72 (4.17%)	7 / 75 (9.33%)	4 / 76 (5.26%)
occurrences (all)	3	7	5
Chills			

subjects affected / exposed	4 / 72 (5.56%)	1 / 75 (1.33%)	7 / 76 (9.21%)
occurrences (all)	4	1	9
Chest pain			
subjects affected / exposed	2 / 72 (2.78%)	4 / 75 (5.33%)	5 / 76 (6.58%)
occurrences (all)	2	4	5
Influenza like illness			
subjects affected / exposed	2 / 72 (2.78%)	5 / 75 (6.67%)	2 / 76 (2.63%)
occurrences (all)	2	6	3
Oedema			
subjects affected / exposed	1 / 72 (1.39%)	3 / 75 (4.00%)	5 / 76 (6.58%)
occurrences (all)	1	3	6
Axillary pain			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	5 / 76 (6.58%)
occurrences (all)	0	0	5
Malaise			
subjects affected / exposed	0 / 72 (0.00%)	2 / 75 (2.67%)	5 / 76 (6.58%)
occurrences (all)	0	4	15
Chest discomfort			
subjects affected / exposed	4 / 72 (5.56%)	3 / 75 (4.00%)	3 / 76 (3.95%)
occurrences (all)	5	4	4
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	6 / 72 (8.33%)	2 / 75 (2.67%)	7 / 76 (9.21%)
occurrences (all)	9	3	11
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	2 / 72 (2.78%)	3 / 75 (4.00%)	6 / 76 (7.89%)
occurrences (all)	2	4	7
Vulvovaginal dryness			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	4 / 76 (5.26%)
occurrences (all)	0	1	4
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	13 / 72 (18.06%)	8 / 75 (10.67%)	10 / 76 (13.16%)
occurrences (all)	15	9	11
Epistaxis			

subjects affected / exposed	8 / 72 (11.11%)	10 / 75 (13.33%)	11 / 76 (14.47%)
occurrences (all)	12	12	16
Cough			
subjects affected / exposed	10 / 72 (13.89%)	8 / 75 (10.67%)	10 / 76 (13.16%)
occurrences (all)	14	9	12
Oropharyngeal pain			
subjects affected / exposed	7 / 72 (9.72%)	6 / 75 (8.00%)	9 / 76 (11.84%)
occurrences (all)	7	9	15
Rhinorrhoea			
subjects affected / exposed	3 / 72 (4.17%)	5 / 75 (6.67%)	7 / 76 (9.21%)
occurrences (all)	5	5	7
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 72 (16.67%)	13 / 75 (17.33%)	17 / 76 (22.37%)
occurrences (all)	14	13	22
Depression			
subjects affected / exposed	3 / 72 (4.17%)	3 / 75 (4.00%)	4 / 76 (5.26%)
occurrences (all)	3	3	4
Anxiety			
subjects affected / exposed	1 / 72 (1.39%)	4 / 75 (5.33%)	4 / 76 (5.26%)
occurrences (all)	1	5	4
Investigations			
Haemoglobin decreased			
subjects affected / exposed	6 / 72 (8.33%)	4 / 75 (5.33%)	7 / 76 (9.21%)
occurrences (all)	7	8	8
Alanine aminotransferase increased			
subjects affected / exposed	5 / 72 (6.94%)	3 / 75 (4.00%)	8 / 76 (10.53%)
occurrences (all)	5	5	10
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 72 (5.56%)	3 / 75 (4.00%)	5 / 76 (6.58%)
occurrences (all)	4	4	5
Weight decreased			
subjects affected / exposed	3 / 72 (4.17%)	4 / 75 (5.33%)	5 / 76 (6.58%)
occurrences (all)	3	5	5
Injury, poisoning and procedural complications			

Radiation skin injury			
subjects affected / exposed	11 / 72 (15.28%)	14 / 75 (18.67%)	7 / 76 (9.21%)
occurrences (all)	14	16	7
Seroma			
subjects affected / exposed	4 / 72 (5.56%)	4 / 75 (5.33%)	1 / 76 (1.32%)
occurrences (all)	5	4	2
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	7 / 72 (9.72%)	8 / 75 (10.67%)	7 / 76 (9.21%)
occurrences (all)	12	12	10
Palpitations			
subjects affected / exposed	3 / 72 (4.17%)	1 / 75 (1.33%)	4 / 76 (5.26%)
occurrences (all)	3	1	5
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 72 (27.78%)	15 / 75 (20.00%)	16 / 76 (21.05%)
occurrences (all)	30	23	20
Dysgeusia			
subjects affected / exposed	8 / 72 (11.11%)	10 / 75 (13.33%)	16 / 76 (21.05%)
occurrences (all)	10	11	22
Dizziness			
subjects affected / exposed	7 / 72 (9.72%)	9 / 75 (12.00%)	15 / 76 (19.74%)
occurrences (all)	12	11	21
Neuropathy peripheral			
subjects affected / exposed	5 / 72 (6.94%)	4 / 75 (5.33%)	8 / 76 (10.53%)
occurrences (all)	5	4	10
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 72 (5.56%)	8 / 75 (10.67%)	5 / 76 (6.58%)
occurrences (all)	12	14	10
Polyneuropathy			
subjects affected / exposed	4 / 72 (5.56%)	1 / 75 (1.33%)	4 / 76 (5.26%)
occurrences (all)	4	1	4
Paraesthesia			
subjects affected / exposed	3 / 72 (4.17%)	4 / 75 (5.33%)	9 / 76 (11.84%)
occurrences (all)	3	7	11
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	36 / 72 (50.00%)	33 / 75 (44.00%)	37 / 76 (48.68%)
occurrences (all)	102	86	107
Anaemia			
subjects affected / exposed	14 / 72 (19.44%)	8 / 75 (10.67%)	29 / 76 (38.16%)
occurrences (all)	17	11	48
Leukopenia			
subjects affected / exposed	16 / 72 (22.22%)	12 / 75 (16.00%)	13 / 76 (17.11%)
occurrences (all)	61	37	36
Thrombocytopenia			
subjects affected / exposed	5 / 72 (6.94%)	1 / 75 (1.33%)	23 / 76 (30.26%)
occurrences (all)	8	1	40
Febrile neutropenia			
subjects affected / exposed	4 / 72 (5.56%)	3 / 75 (4.00%)	2 / 76 (2.63%)
occurrences (all)	4	3	2
Eye disorders			
Lacrimation increased			
subjects affected / exposed	9 / 72 (12.50%)	4 / 75 (5.33%)	6 / 76 (7.89%)
occurrences (all)	11	5	6
Eyelid oedema			
subjects affected / exposed	1 / 72 (1.39%)	1 / 75 (1.33%)	4 / 76 (5.26%)
occurrences (all)	1	1	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	46 / 72 (63.89%)	44 / 75 (58.67%)	55 / 76 (72.37%)
occurrences (all)	91	68	129
Nausea			
subjects affected / exposed	38 / 72 (52.78%)	41 / 75 (54.67%)	34 / 76 (44.74%)
occurrences (all)	84	71	71
Vomiting			
subjects affected / exposed	29 / 72 (40.28%)	27 / 75 (36.00%)	30 / 76 (39.47%)
occurrences (all)	44	36	60
Dyspepsia			
subjects affected / exposed	19 / 72 (26.39%)	9 / 75 (12.00%)	17 / 76 (22.37%)
occurrences (all)	21	9	21
Constipation			

subjects affected / exposed	14 / 72 (19.44%)	18 / 75 (24.00%)	13 / 76 (17.11%)
occurrences (all)	21	25	19
Abdominal pain upper			
subjects affected / exposed	7 / 72 (9.72%)	6 / 75 (8.00%)	5 / 76 (6.58%)
occurrences (all)	8	9	8
Abdominal pain			
subjects affected / exposed	3 / 72 (4.17%)	7 / 75 (9.33%)	6 / 76 (7.89%)
occurrences (all)	3	8	9
Dry mouth			
subjects affected / exposed	4 / 72 (5.56%)	2 / 75 (2.67%)	8 / 76 (10.53%)
occurrences (all)	4	2	9
Haemorrhoids			
subjects affected / exposed	5 / 72 (6.94%)	1 / 75 (1.33%)	4 / 76 (5.26%)
occurrences (all)	5	1	4
Abdominal distension			
subjects affected / exposed	2 / 72 (2.78%)	2 / 75 (2.67%)	4 / 76 (5.26%)
occurrences (all)	2	2	4
Oral pain			
subjects affected / exposed	1 / 72 (1.39%)	4 / 75 (5.33%)	2 / 76 (2.63%)
occurrences (all)	1	5	2
Stomatitis			
subjects affected / exposed	10 / 72 (13.89%)	13 / 75 (17.33%)	9 / 76 (11.84%)
occurrences (all)	12	19	10
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	35 / 72 (48.61%)	39 / 75 (52.00%)	42 / 76 (55.26%)
occurrences (all)	35	39	45
Rash			
subjects affected / exposed	17 / 72 (23.61%)	8 / 75 (10.67%)	20 / 76 (26.32%)
occurrences (all)	18	13	20
Nail disorder			
subjects affected / exposed	9 / 72 (12.50%)	8 / 75 (10.67%)	10 / 76 (13.16%)
occurrences (all)	9	9	13
Erythema			
subjects affected / exposed	10 / 72 (13.89%)	5 / 75 (6.67%)	11 / 76 (14.47%)
occurrences (all)	10	6	15

Dry skin			
subjects affected / exposed	5 / 72 (6.94%)	7 / 75 (9.33%)	8 / 76 (10.53%)
occurrences (all)	6	7	11
Palmar -plantar erythrodysaesthesia syndrome			
subjects affected / exposed	5 / 72 (6.94%)	9 / 75 (12.00%)	6 / 76 (7.89%)
occurrences (all)	7	9	6
Pruritus			
subjects affected / exposed	3 / 72 (4.17%)	7 / 75 (9.33%)	4 / 76 (5.26%)
occurrences (all)	4	10	5
Skin reaction			
subjects affected / exposed	2 / 72 (2.78%)	5 / 75 (6.67%)	3 / 76 (3.95%)
occurrences (all)	2	5	3
Dermatitis			
subjects affected / exposed	1 / 72 (1.39%)	5 / 75 (6.67%)	0 / 76 (0.00%)
occurrences (all)	1	5	0
Hyperhidrosis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	5 / 76 (6.58%)
occurrences (all)	1	0	6
Night sweats			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	5 / 76 (6.58%)
occurrences (all)	1	0	6
Skin hyperpigmentation			
subjects affected / exposed	2 / 72 (2.78%)	4 / 75 (5.33%)	0 / 76 (0.00%)
occurrences (all)	2	5	0
Skin exfoliation			
subjects affected / exposed	0 / 72 (0.00%)	4 / 75 (5.33%)	0 / 76 (0.00%)
occurrences (all)	0	4	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 72 (2.78%)	0 / 75 (0.00%)	7 / 76 (9.21%)
occurrences (all)	2	0	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 72 (25.00%)	18 / 75 (24.00%)	11 / 76 (14.47%)
occurrences (all)	22	24	12
Myalgia			

subjects affected / exposed	14 / 72 (19.44%)	16 / 75 (21.33%)	8 / 76 (10.53%)
occurrences (all)	21	22	14
Back pain			
subjects affected / exposed	11 / 72 (15.28%)	9 / 75 (12.00%)	7 / 76 (9.21%)
occurrences (all)	15	10	7
Musculoskeletal pain			
subjects affected / exposed	11 / 72 (15.28%)	8 / 75 (10.67%)	5 / 76 (6.58%)
occurrences (all)	13	11	5
Pain in extremity			
subjects affected / exposed	7 / 72 (9.72%)	7 / 75 (9.33%)	7 / 76 (9.21%)
occurrences (all)	7	8	7
Muscle spasms			
subjects affected / exposed	4 / 72 (5.56%)	4 / 75 (5.33%)	6 / 76 (7.89%)
occurrences (all)	5	4	7
Musculoskeletal chest pain			
subjects affected / exposed	5 / 72 (6.94%)	3 / 75 (4.00%)	5 / 76 (6.58%)
occurrences (all)	6	3	7
Bone pain			
subjects affected / exposed	4 / 72 (5.56%)	4 / 75 (5.33%)	2 / 76 (2.63%)
occurrences (all)	4	4	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 72 (8.33%)	9 / 75 (12.00%)	9 / 76 (11.84%)
occurrences (all)	7	13	9
Upper respiratory tract infection			
subjects affected / exposed	7 / 72 (9.72%)	10 / 75 (13.33%)	3 / 76 (3.95%)
occurrences (all)	10	13	5
Urinary tract infection			
subjects affected / exposed	5 / 72 (6.94%)	7 / 75 (9.33%)	7 / 76 (9.21%)
occurrences (all)	5	7	11
Rhinitis			
subjects affected / exposed	6 / 72 (8.33%)	1 / 75 (1.33%)	4 / 76 (5.26%)
occurrences (all)	8	1	5
Cystitis			
subjects affected / exposed	0 / 72 (0.00%)	4 / 75 (5.33%)	6 / 76 (7.89%)
occurrences (all)	0	4	7

Conjunctivitis			
subjects affected / exposed	3 / 72 (4.17%)	2 / 75 (2.67%)	4 / 76 (5.26%)
occurrences (all)	3	2	4
Influenza			
subjects affected / exposed	5 / 72 (6.94%)	4 / 75 (5.33%)	2 / 76 (2.63%)
occurrences (all)	5	4	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 72 (20.83%)	8 / 75 (10.67%)	16 / 76 (21.05%)
occurrences (all)	18	11	27

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2010	The protocol has been amended to accommodate following changes: 1. The protocol requirement for a mammogram between study day -14 and start of treatment was a significant issue for many centres. Many subjects would have had a mammogram before study day -14 and concerns were raised over repeat exposure to radiation within a short timeframe which would not be in the subject's interest and could be potentially harmful. An extension of the window for the mammogram to be performed in screening period has been made to remove need for a second 'study' mammogram if subject has recently received a mammogram as part of standard practice. In addition, centres will be able to use magnetic resonance imaging in place of mammography according to local practice. 2. To provide information on the 'Emergency Medical Call Centre Help Desk' for medical emergencies outside regular business hours. 3. To clarify schedule of electrocardiogram assessments in treatment period of study, information on suspected unexpected serious adverse reaction reporting, need for clinical breast exam and mammogram at end of Cycle 6 and prior to surgery, clarification of complete blood count assessment schedule by treatment arm in neoadjuvant period of study. 4. Clarification that Steering Committee will also look at key safety outputs from the neoadjuvant portion of the study. 5. To clarify that investigators may adjust dose of study medications based upon small changes in body weight or body surface area. 6. Clarification of modifications of dosing of non-investigational medicinal products.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported