Clinical trial results:
A Randomized, Double-blind, Phase 3 Study Evaluating the Efficacy and Safety of ABP 980 Compared With Trastuzumab in Subjects With HER2 Positive Early Breast Cancer

Summary

EudraCT number	2012-004319-29
Trial protocol	GB DE HU SK IT CZ ES GR BG PL RO
Global end of trial date	27 January 2017

Results information

Result version number	v1 (current)
This version publication date	01 February 2018
First version publication date	01 February 2018

Trial information

Trial identification

Sponsor protocol code	20120283

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01901146
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 01320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	27 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the treatment effect of ABP 980 with trastuzumab on pathologic complete response (pCR) in women with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer.

Protection of trial subjects:

This study was conducted in compliance with independent ethics committees (IECs), institutional review boards (IRBs), and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, in accordance with applicable regulations regarding clinical safety data management (E2A, E2B [R3]), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9 and E10).
The investigator explained the benefits and risks of participation in the study to each subject or the subject's legally acceptable representative or impartial witness and obtained written informed consent. Written informed consent was required to be obtained before the subject entering the study and before initiation of any study-related procedure.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 238
Country: Number of subjects enrolled	Ukraine: 66
Country: Number of subjects enrolled	Poland: 57
Country: Number of subjects enrolled	Belarus: 52
Country: Number of subjects enrolled	Romania: 44
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Serbia: 27
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Mexico: 37
Country: Number of subjects enrolled	South Africa: 28
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Chile: 3

Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	725
EEA total number of subjects	250

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)	622
From 65 to 84 years	102
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 123 sites in 20 countries from April 2013 to January 2017. The study consisted of a neoadjuvant treatment phase for 4 cycles, surgery, and adjuvant treatment for up to one year from the first day of investigational product (IP) administration in the neoadjuvant phase.

Pre-assignment

Screening details:

Enrolled patients received run-in chemotherapy consisting of epirubicin and cyclophosphamide every 3 weeks for 4 cycles. After the run-in, participants with adequate cardiac function were randomized. Randomization was stratified by tumor stage, nodal status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.

Period 1

Period 1 title	Neoadjuvant Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	ABP 980

Arm description:

Participants received ABP 980 at an initial dose of 8 mg/kg over a 90-minute intravenous (IV) infusion, then 6 mg/kg IV infusion every 3 weeks (Q3W) for 3 additional cycles plus paclitaxel at 175 mg/m² Q3W for 4 cycles.

Arm type	Experimental
Investigational medicinal product name	ABP 980
Investigational medicinal product code	ABP 980
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

ABP 980 was administered at an initial dose of 8 mg/kg over a 90-minute intravenous (IV) infusion, then 6 mg/kg IV infusion Q3W for 3 additional cycles.

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

Dosage and administration details:

Paclitaxel, 175 mg/m² Q3W for 4 cycles (or 80 mg/m² QW for 12 cycles, if local standard of care).

Arm title	Trastuzumab

Arm description:

Participants received trastuzumab at an initial dose of 8 mg/kg over a 90-minute IV infusion, then 6 mg/kg IV infusion Q3W for 3 additional cycles plus paclitaxel at 175 mg/m² Q3W for 4 cycles.

Arm type	Active comparator

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered at an initial dose of 8 mg/kg over a 90-minute IV infusion, then 6 mg/kg IV infusion Q3W for 3 additional cycles.

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

Dosage and administration details:

Paclitaxel, 175 mg/m² Q3W for 4 cycles (or 80 mg/m² QW for 12 cycles, if local standard of care).

Number of subjects in period 1	ABP 980	Trastuzumab
Started	364	361
Completed	358	347
Not completed	6	14
Physician decision	1	2
Consent withdrawn by subject	2	5
Death	1	2
Disease progression or recurrence	2	3
Lost to follow-up	-	1
Requirement for alternative therapy	-	1

Period 2

Period 2 title	Adjuvant Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	ABP 980/ABP 980

Arm description:

After surgery, participants initially randomized to ABP 980 continued to receive ABP 980 at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day of investigational product administration in the neoadjuvant phase.

Arm type	Experimental

Investigational medicinal product name	ABP 980
Investigational medicinal product code	ABP 980
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

ABP 980 was administered at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day investigational product was administered in the neoadjuvant phase. At the start of the adjuvant phase, if the first dose of ABP 980 was > 4 weeks from the last dose of investigational product administered in the neoadjuvant phase, then the first dose was to be administered as a re-loading dose of 8 mg/kg.

Arm title	Trastuzumab/Trastuzumab

Arm description:

After surgery, participants originally randomized to trastuzumab were re-randomized and continued to receive trastuzumab at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day of investigational product administration in the neoadjuvant phase.

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day investigational product was administered in the neoadjuvant phase. At the start of the adjuvant phase if the first dose of trastuzumab was > 4 weeks from the last dose of trastuzumab administered in the neoadjuvant phase, then the first dose of investigational product was administered as a re-loading dose at 8 mg/kg.

Arm title	Trastuzumab/ABP 980

Arm description:

After surgery, participants originally randomized to trastuzumab were re-randomized and switched to receive ABP 980 at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day of investigational product administration in the neoadjuvant phase.

Arm type	Experimental
Investigational medicinal product name	ABP 980
Investigational medicinal product code	ABP 980
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

ABP 980 was administered at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day investigational product was administered in the neoadjuvant phase. At the start of the adjuvant phase, if the first dose of ABP 980 was > 4 weeks from the last dose of investigational product administered in the neoadjuvant phase, then the first dose was to be administered as a re-loading dose of 8 mg/kg.

Number of subjects in period 2[1]	ABP 980/ABP 980	Trastuzumab/Trastuzumab	Trastuzumab/ABP 980
Started	349	171	171
Completed	323	164	157
Not completed	26	7	14
Physician decision	9	2	4
Consent withdrawn by subject	4	1	4

Other	1	-	-
Death	-	-	3
Disease progression or recurrence	12	4	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Fourteen subjects discontinued the study after surgery but before entering the adjuvant phase.

Baseline characteristics

Reporting groups	
Reporting group title	ABP 980
Reporting group description:	
Participants received ABP 980 at an initial dose of 8 mg/kg over a 90-minute intravenous (IV) infusion, then 6 mg/kg IV infusion every 3 weeks (Q3W) for 3 additional cycles plus paclitaxel at 175 mg/m² Q3W for 4 cycles.	
Reporting group title	Trastuzumab
Reporting group description:	
Participants received trastuzumab at an initial dose of 8 mg/kg over a 90-minute IV infusion, then 6 mg/kg IV infusion Q3W for 3 additional cycles plus paclitaxel at 175 mg/m² Q3W for 4 cycles.	

Reporting group values	ABP 980	Trastuzumab	Total
Number of subjects	364	361	725
Age Categorical Units: Subjects			
< 50 years	140	134	274
≥ 50 years	224	227	451
Age Continuous Units: years			
arithmetic mean	52.8	52.7	
standard deviation	± 10.72	± 11.29	-
Gender Categorical Units: Subjects			
Female	364	361	725
Male	0	0	0
Race Units: Subjects			
White	331	333	664
Black or African American	10	4	14
Asian	2	3	5
American Indian or Alaska Native	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0
Other	20	21	41
Ethnicity Units: Subjects			
Hispanic or Latino	32	36	68
Not Hispanic or Latino	332	324	656
Not allowed to collect	0	1	1
Tumor Stage Units: Subjects			
< T 4	282	281	563
T4	82	80	162
Axilla Lymph Node Involvement Units: Subjects			
Yes	277	266	543
No	87	95	182
Hormone Receptor Status			

Units: Subjects			
Estrogen and/or progesterone receptor positive	265	268	533
Estrogen and progesterone receptor negative	99	93	192
Paclitaxel Dosing Schedule Units: Subjects			
Every 3 weeks	256	258	514
Every week	108	103	211
Geographic Region Units: Subjects			
Eastern Europe	271	273	544
Western Europe	43	46	89
Other	50	42	92

End points

End points reporting groups

Reporting group title	ABP 980
Reporting group description:	
Participants received ABP 980 at an initial dose of 8 mg/kg over a 90-minute intravenous (IV) infusion, then 6 mg/kg IV infusion every 3 weeks (Q3W) for 3 additional cycles plus paclitaxel at 175 mg/m² Q3W for 4 cycles.	
Reporting group title	Trastuzumab
Reporting group description:	
Participants received trastuzumab at an initial dose of 8 mg/kg over a 90-minute IV infusion, then 6 mg/kg IV infusion Q3W for 3 additional cycles plus paclitaxel at 175 mg/m² Q3W for 4 cycles.	
Reporting group title	ABP 980/ABP 980
Reporting group description:	
After surgery, participants initially randomized to ABP 980 continued to receive ABP 980 at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day of investigational product administration in the neoadjuvant phase.	
Reporting group title	Trastuzumab/Trastuzumab
Reporting group description:	
After surgery, participants originally randomized to trastuzumab were re-randomized and continued to receive trastuzumab at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day of investigational product administration in the neoadjuvant phase.	
Reporting group title	Trastuzumab/ABP 980
Reporting group description:	
After surgery, participants originally randomized to trastuzumab were re-randomized and switched to receive ABP 980 at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day of investigational product administration in the neoadjuvant phase.	

Primary: Percentage of Participants with a Pathologic Complete Response

End point title	Percentage of Participants with a Pathologic Complete Response
End point description:	
Pathologic complete response (pCR) was defined as the absence of invasive tumor cells in the breast tissue and in axillary lymph nodes, regardless of residual ductal carcinoma in situ (DCIS). The primary efficacy analysis was based on local pathology evaluation of the tumor samples using the pCR evaluable population, which included all randomized subjects who received any amount of investigational product, underwent the surgery, and had a non-missing evaluable pCR assessment from the local laboratory evaluation.	
End point type	Primary
End point timeframe:	
3 to 7 weeks after the last dose of investigational product in the neoadjuvant phase	

End point values	ABP 980	Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358[1]	338[2]		
Units: percentage of participants				
number (not applicable)	48.0	40.5		

Notes:

[1] - pCR Evaluable Population

[2] - pCR Evaluable Population

Statistical analyses

Statistical analysis title	Risk Difference Analysis

Statistical analysis description:

The clinical equivalence between ABP 980 and trastuzumab was first evaluated by comparing the 2-sided 90% CI of the risk difference (RD) of pCR between ABP 980 and trastuzumab estimated using a generalized linear model adjusted for stratification factors, with the margin of (-13%, 13%).

Comparison groups	ABP 980 v Trastuzumab
Number of subjects included in analysis	696
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0508 [3]
Method	Generalized linear model
Parameter estimate	Risk difference (RD)
Point estimate	7.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.2
upper limit	13.4

Notes:

[3] - Generalized linear model adjusted for the randomization stratification factors tumor(T)-stage, nodal status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.

Statistical analysis title	Risk Ratio Analysis

Statistical analysis description:

If the test of equivalence on the RD of pCR was successful, then equivalence was tested on the risk ratio (RR) of pCR at a 2-sided significance level of 0.05 by comparing the 2-sided 90% CI of the RR of pCR between ABP 980 and trastuzumab estimated using a generalized linear model adjusted for stratification factors, with the margin of (0.7586, 1/0.7586). If the test of equivalence on the RD was not successful, the RR of pCR and 90% CI were considered to be descriptive.

Comparison groups	ABP 980 v Trastuzumab
Number of subjects included in analysis	696
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.043 [4]
Method	Generalized linear model
Parameter estimate	Risk ratio (RR)
Point estimate	1.1877
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.0327
upper limit	1.366

Notes:

[4] - Generalized linear model adjusted for the randomization stratification factors T-stage, node status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.

Secondary: Percentage of Participants with a Pathologic Complete Response in Breast Tissue Only

End point title	Percentage of Participants with a Pathologic Complete Response in Breast Tissue Only

End point description:

Pathologic complete response (pCR) was defined as the absence of invasive tumor cells in the breast tissue, regardless of residual ductal carcinoma in situ (DCIS).
The primary efficacy analysis was based on local pathology evaluation of the tumor samples using the pCR evaluable population, which included all randomized subjects who received any amount of investigational product, underwent the surgery, and had a non-missing evaluable pCR assessment from the local laboratory evaluation.

End point type	Secondary

End point timeframe:

3 to 7 weeks after the last dose of investigational product in the neoadjuvant phase

End point values	ABP 980	Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358[5]	338[6]		
Units: percentage of participants				
number (not applicable)	51.1	45.0		

Notes:

[5] - pCR Evaluable Population

[6] - pCR Evaluable Population

Statistical analyses

Statistical analysis title	Risk Ratio Analysis
Comparison groups	ABP 980 v Trastuzumab
Number of subjects included in analysis	696
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0807 [7]
Method	Generalized linear model
Parameter estimate	Risk ratio (RR)
Point estimate	1.1463
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.008
upper limit	1.3035

Notes:

[7] - Generalized linear model adjusted for the randomization stratification factors T-stage, node status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.

Statistical analysis title	Risk Difference Analysis
Comparison groups	ABP 980 v Trastuzumab

Number of subjects included in analysis	696
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1086 [8]
Method	Generalized linear model
Parameter estimate	Risk difference (RD)
Point estimate	6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.2
upper limit	12.2

Notes:

[8] - Generalized linear model adjusted for the randomization stratification factors T-stage, node status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.

Secondary: Percentage of Participants with a Pathologic Complete Response in Breast Tissue and Axillary Lymph Nodes and Absence of DCIS

End point title	Percentage of Participants with a Pathologic Complete Response in Breast Tissue and Axillary Lymph Nodes and Absence of DCIS

End point description:

Pathological complete response was defined as the absence of invasive tumor cells in the breast tissue and axillary lymph node(s) and absence of residual DCIS.
The analysis was based on local pathology evaluation of the tumor samples using the pCR evaluable population, which included all randomized subjects who received any amount of investigational product, underwent the surgery, and had a non-missing evaluable pCR assessment from the local laboratory evaluation.

End point type	Secondary

End point timeframe:

3 to 7 weeks after the last dose of investigational product in the neoadjuvant phase

End point values	ABP 980	Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	358[9]	338[10]		
Units: percentage of participants				
number (not applicable)	37.7	29.6		

Notes:

[9] - pCR Evaluable Population

[10] - pCR Evaluable Population

Statistical analyses

Statistical analysis title	Risk Difference Analysis
Comparison groups	ABP 980 v Trastuzumab

Number of subjects included in analysis	696
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0253 [11]
Method	Generalized linear model
Parameter estimate	Risk difference (RD)
Point estimate	8
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.1
upper limit	13.9

Notes:

[11] - Generalized linear model adjusted for the randomization stratification factors T-stage, node status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.

Statistical analysis title	Risk Ratio Analysis
Comparison groups	ABP 980 v Trastuzumab
Number of subjects included in analysis	696
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0245 [12]
Method	Generalized linear model
Parameter estimate	Risk ratio (RR)
Point estimate	1.2746
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.0673
upper limit	1.5222

Notes:

[12] - Generalized linear model adjusted for the randomization stratification factors T-stage, node status, hormone receptor status, planned paclitaxel dosing schedule, and geographic region.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Neoadjuvant phase: From the first dose of IP to 30 days after last dose in the neoadjuvant phase or the start of adjuvant phase; up to 16 weeks.
Adjuvant phase: From the first dose of IP after surgery until 30 days after last dose; approximately 40 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Neoadjuvant Phase: Trastuzumab

Reporting group description:

Participants received trastuzumab at an initial dose of 8 mg/kg over a 90-minute IV infusion, then 6 mg/kg IV infusion Q3W for 3 additional cycles plus paclitaxel at 175 mg/m² Q3W for 4 cycles.

Reporting group title	Neoadjuvant Phase: ABP 980

Reporting group description:

Participants received ABP 980 at an initial dose of 8 mg/kg over a 90-minute intravenous (IV) infusion, then 6 mg/kg IV infusion every 3 weeks (Q3W) for 3 additional cycles plus paclitaxel at 175 mg/m² Q3W for 4 cycles.

Reporting group title	Adjuvant Phase: Trastuzumab/Trastuzumab

Reporting group description:

After surgery, participants originally randomized to trastuzumab continued to receive trastuzumab at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day of investigational product administration in the neoadjuvant phase.

Reporting group title	Adjuvant Phase: Trastuzumab/ABP 980

Reporting group description:

After surgery, participants originally randomized to trastuzumab were switched to receive ABP 980 at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day of investigational product administration in the neoadjuvant phase.

Reporting group title	Adjuvant Phase: ABP 980/ABP 980

Reporting group description:

After surgery, participants initially randomized to ABP 980 continued to receive ABP 980 at a dose of 6 mg/kg IV infusion Q3W for up to 1 year from the first day of investigational product administration in the neoadjuvant phase.

Serious adverse events	Neoadjuvant Phase: Trastuzumab	Neoadjuvant Phase: ABP 980	Adjuvant Phase: Trastuzumab/Trastuzumab
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 361 (1.39%)	18 / 364 (4.95%)	6 / 171 (3.51%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to adrenals			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Surgical and medical procedures			

Hysterectomy			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Gait disturbance			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Hydrothorax			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	1 / 361 (0.28%)	0 / 364 (0.00%)	0 / 171 (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
Bipolar disorder			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 361 (0.28%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

White blood cell count decreased			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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			
Drug dispensing error			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation pneumonitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Subcutaneous haematoma			
subjects affected / exposed	1 / 361 (0.28%)	0 / 364 (0.00%)	0 / 171 (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
Tibia fracture			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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 limb fracture			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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 decomposition			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Sinus bradycardia			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Headache			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 361 (0.00%)	3 / 364 (0.82%)	0 / 171 (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
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer perforation			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal toxicity			
subjects affected / exposed	1 / 361 (0.28%)	0 / 364 (0.00%)	0 / 171 (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
Pancreatitis acute			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	1 / 361 (0.28%)	0 / 364 (0.00%)	0 / 171 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Incision site infection			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 361 (0.00%)	2 / 364 (0.55%)	2 / 171 (1.17%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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
Septic shock			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	1 / 171 (0.58%)
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	0 / 361 (0.00%)	0 / 364 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound sepsis			
subjects affected / exposed	1 / 361 (0.28%)	0 / 364 (0.00%)	0 / 171 (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			
Decreased appetite			
subjects affected / exposed	0 / 361 (0.00%)	1 / 364 (0.27%)	0 / 171 (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

Serious adverse events	Adjuvant Phase: Trastuzumab/ABP 980	Adjuvant Phase: ABP 980/ABP 980	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 171 (3.51%)	18 / 349 (5.16%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to adrenals			
subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Hysterectomy			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

White blood cell count decreased			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Drug dispensing error			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Upper limb fracture			
subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound decomposition			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Headache			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site infection			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 171 (0.58%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 171 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 171 (0.00%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Neoadjuvant Phase: Trastuzumab	Neoadjuvant Phase: ABP 980	Adjuvant Phase: Trastuzumab/Trastuzumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	220 / 361 (60.94%)	227 / 364 (62.36%)	49 / 171 (28.65%)
Injury, poisoning and procedural complications			
Radiation skin injury			

subjects affected / exposed	0 / 361 (0.00%)	0 / 364 (0.00%)	17 / 171 (9.94%)
occurrences (all)	0	0	21
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	43 / 361 (11.91%)	51 / 364 (14.01%)	3 / 171 (1.75%)
occurrences (all)	64	65	3
Paraesthesia			
subjects affected / exposed	21 / 361 (5.82%)	17 / 364 (4.67%)	0 / 171 (0.00%)
occurrences (all)	34	26	0
Peripheral sensory neuropathy			
subjects affected / exposed	22 / 361 (6.09%)	25 / 364 (6.87%)	0 / 171 (0.00%)
occurrences (all)	29	31	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	38 / 361 (10.53%)	40 / 364 (10.99%)	7 / 171 (4.09%)
occurrences (all)	61	54	10
Leukopenia			
subjects affected / exposed	16 / 361 (4.43%)	21 / 364 (5.77%)	5 / 171 (2.92%)
occurrences (all)	20	26	10
Neutropenia			
subjects affected / exposed	45 / 361 (12.47%)	53 / 364 (14.56%)	10 / 171 (5.85%)
occurrences (all)	75	81	15
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	59 / 361 (16.34%)	54 / 364 (14.84%)	7 / 171 (4.09%)
occurrences (all)	120	113	8
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	19 / 361 (5.26%)	23 / 364 (6.32%)	2 / 171 (1.17%)
occurrences (all)	21	35	3
Nausea			
subjects affected / exposed	18 / 361 (4.99%)	21 / 364 (5.77%)	3 / 171 (1.75%)
occurrences (all)	39	28	4
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	23 / 361 (6.37%)	19 / 364 (5.22%)	0 / 171 (0.00%)
occurrences (all)	24	19	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	55 / 361 (15.24%)	63 / 364 (17.31%)	9 / 171 (5.26%)
occurrences (all)	138	145	9
Bone pain			
subjects affected / exposed	29 / 361 (8.03%)	12 / 364 (3.30%)	0 / 171 (0.00%)
occurrences (all)	62	24	0
Myalgia			
subjects affected / exposed	31 / 361 (8.59%)	34 / 364 (9.34%)	3 / 171 (1.75%)
occurrences (all)	50	54	3

Non-serious adverse events	Adjuvant Phase: Trastuzumab/ABP 980	Adjuvant Phase: ABP 980/ABP 980	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 171 (35.09%)	124 / 349 (35.53%)	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	16 / 171 (9.36%)	37 / 349 (10.60%)	
occurrences (all)	16	41	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	2 / 171 (1.17%)	8 / 349 (2.29%)	
occurrences (all)	2	9	
Paraesthesia			
subjects affected / exposed	1 / 171 (0.58%)	6 / 349 (1.72%)	
occurrences (all)	1	7	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 171 (0.00%)	3 / 349 (0.86%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 171 (5.85%)	17 / 349 (4.87%)	
occurrences (all)	19	24	
Leukopenia			

subjects affected / exposed	8 / 171 (4.68%)	15 / 349 (4.30%)	
occurrences (all)	17	24	
Neutropenia			
subjects affected / exposed	6 / 171 (3.51%)	25 / 349 (7.16%)	
occurrences (all)	8	52	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 171 (5.85%)	17 / 349 (4.87%)	
occurrences (all)	10	23	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 171 (2.34%)	9 / 349 (2.58%)	
occurrences (all)	5	9	
Nausea			
subjects affected / exposed	2 / 171 (1.17%)	11 / 349 (3.15%)	
occurrences (all)	2	18	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 171 (1.17%)	3 / 349 (0.86%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 171 (5.26%)	20 / 349 (5.73%)	
occurrences (all)	11	24	
Bone pain			
subjects affected / exposed	3 / 171 (1.75%)	1 / 349 (0.29%)	
occurrences (all)	5	1	
Myalgia			
subjects affected / exposed	2 / 171 (1.17%)	2 / 349 (0.57%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2012	The primary purpose of the change in version 1.1 (08 October 2012) was administrative.
21 May 2013	The primary purposes of changes in version 2.0 were the following: - to update the power calculations to reflect updated assumptions, including increasing the number of subjects and sites and the duration of the study - to add RD of pCR in breast tissue and axillary lymph nodes as a co-primary endpoint and make appropriate updates to the statistical methods, including sequential testing - to add RD of pCR in breast tissue and RD of pCR in breast tissue and axillary lymph nodes and absence of DCIS as secondary endpoints - to define a pCR evaluable population - to modify the restrictions on chemotherapy pretreatment regimens and treatment regimens for chemotherapy-associated toxicities to accommodate differing international standards - to specify that adequate cardiac function is required after run-in chemotherapy for starting treatment with investigational product; at all indicated visits, echocardiogram was required and results were required to be obtained before treatment with investigational product - to delete the option for a third dose decrease in the case of grade 2 hepatic toxicities - to specify that the formal interim analysis would be performed when 1/3 of subjects had been assessed for pCR
06 August 2015	The primary purposes of the changes in version 3.0 were the following: - to revise the period of required contraception use for women of childbearing potential, to 7 months after the last dose of study drug - to allow dose to be recalculated for subjects who underwent a > 10% change in weight from baseline - to update the statistical sections, including definitions of the analysis populations, to incorporate feedback received from agencies at that time - to allow flexibility in use the of granulocyte-colony stimulating factor (GCSF) to reflect different international standards

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported