Clinical trial results:
A Phase III, Randomized Open-Label Study to Compare Pharmacokinetics, Efficacy and Safety of Subcutaneous (SC) Trastuzumab With Intravenous (IV) Trastuzumab Administered in Women With HER2-Positive Early Breast Cancer (EBC)

Summary

EudraCT number	2008-007326-19
Trial protocol	FR ES CZ EE DE GB SE IT SK HU
Global end of trial date	24 January 2017

Results information

Result version number	v2 (current)
This version publication date	05 January 2018
First version publication date	26 June 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BO22227

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00950300
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the following parameters between Herceptin (trastuzumab) IV and Herceptin SC in the neoadjuvant setting: a) Serum trough concentrations observed pre-surgery; b) Efficacy (pathological complete response)

Protection of trial subjects:

The investigator was required to ensure that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study had to fully adhere to the principles outlined in "Guideline for Good Clinical Practice" International Council for Harmonization (ICH) Tripartite Guideline [January 1997] or with local law if it afforded greater protection to the participant. The investigator was also required to ensure compliance with the European Union Clinical Trial Directive [2001/20/EC] and/or Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 October 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Thailand: 28
Country: Number of subjects enrolled	Peru: 27
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Czech Republic: 17
Country: Number of subjects enrolled	Slovakia: 12
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Panama: 8
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	China: 6
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Guatemala: 3
Country: Number of subjects enrolled	Estonia: 1

Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Russian Federation: 134
Country: Number of subjects enrolled	Brazil: 52
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 51
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Taiwan: 37
Country: Number of subjects enrolled	South Africa: 32
Country: Number of subjects enrolled	France: 28
Worldwide total number of subjects	596
EEA total number of subjects	201

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)	540
From 65 to 84 years	56
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 833 participants were screened, out of which, 596 participants were enrolled into the study.

Period 1

Period 1 title	Neoadjuvant/Adjuvant Treatment Periods
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Herceptin IV + Chemotherapy

Arm description:

Participants received eight cycles of Herceptin IV plus chemotherapy prior to surgery and ten cycles of Herceptin IV after surgery. Chemotherapy consisted of docetaxel 75 milligrams per meter-squared (mg/m^2) every 21 days for four cycles followed by 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2 (FEC) every 21 days for four cycles. Herceptin was administered as 8 milligrams per kilogram (mg/kg) on Day 1 and then as 6 mg/kg on Day 22 and every 21 days thereafter. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the Treatment-Free Follow-Up (TFFU) Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the Survival Follow-Up (SFU) Period.

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

Dosage and administration details:

Herceptin was administered as 8 mg/kg (loading dose during Cycle 1) and 6 mg/kg (subsequent cycles) via IV infusion on Day 1 of each 21-day cycle for a total of 18 cycles.

Arm title	Herceptin SC + Chemotherapy

Arm description:

Participants received eight cycles of Herceptin SC plus chemotherapy prior to surgery and ten cycles of Herceptin SC after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as a 600-milligram (mg) fixed dose given every 21 days. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Arm type	Experimental
Investigational medicinal product name	Herceptin SC (Trastuzumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Herceptin was administered as fixed dose 600 mg SC on Day 1 of each 21-day cycle for a total of 18 cycles.

Number of subjects in period 1	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy
Started	299	297
Received Neoadjuvant Treatment	298	297
Underwent Surgery	277	273
Entered Adjuvant Treatment	277	274
Completed	257	255
Not completed	42	42
Violation of Selection Criteria	2	1
Progression of Disease	12	11
Death	1	3
Recurrence of Disease	10	5
Adverse Event or Intercurrent Illness	6	15
Not Specified	1	1
Lost to follow-up	2	1
Participant Refusal/Withdrawal	4	5
Insufficient Therapeutic Response	3	-
Protocol deviation	1	-

Period 2	
Period 2 title	TFFU Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes

Arm title	Herceptin IV + Chemotherapy

Arm description:

Participants received eight cycles of Herceptin IV plus chemotherapy prior to surgery and ten cycles of Herceptin IV after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as 8 mg/kg on Day 1 and then as 6 mg/kg on Day 22 and every 21 days thereafter. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

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

Dosage and administration details:

Herceptin was administered as 8 mg/kg (loading dose during Cycle 1) and 6 mg/kg (subsequent cycles) via IV infusion on Day 1 of each 21-day cycle for a total of 18 cycles.

Arm title	Herceptin SC + Chemotherapy

Arm description:

Participants received eight cycles of Herceptin SC plus chemotherapy prior to surgery and ten cycles of Herceptin SC after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as a 600-mg fixed dose given every 21 days. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Arm type	Experimental
Investigational medicinal product name	Herceptin SC (Trastuzumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Herceptin was administered as fixed dose 600 mg SC on Day 1 of each 21-day cycle for a total of 18 cycles.

Number of subjects in period 2	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy
Started	257	255
Completed	165	161
Not completed	100	107
Death	4	1
Refused Treatment	10	11
Recurrence of Disease	63	72
Not Specified	4	3
Adverse Event or Intercurrent Illness	3	4
Failure to Return	16	16

Joined	8	13
Discontinued Period 1 But Continued in Period 2	8	13

Period 3

Period 3 title	SFU Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Herceptin IV + Chemotherapy

Arm description:

Participants received eight cycles of Herceptin IV plus chemotherapy prior to surgery and ten cycles of Herceptin IV after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as 8 mg/kg on Day 1 and then as 6 mg/kg on Day 22 and every 21 days thereafter. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

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

Dosage and administration details:

Herceptin was administered as 8 mg/kg (loading dose during Cycle 1) and 6 mg/kg (subsequent cycles) via IV infusion on Day 1 of each 21-day cycle for a total of 18 cycles.

Arm title	Herceptin SC + Chemotherapy

Arm description:

Participants received eight cycles of Herceptin SC plus chemotherapy prior to surgery and ten cycles of Herceptin SC after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as a 600-mg fixed dose given every 21 days. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Arm type	Experimental
Investigational medicinal product name	Herceptin SC (Trastuzumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Herceptin was administered as fixed dose 600 mg SC on Day 1 of each 21-day cycle for a total of 18 cycles.

Number of subjects in period 3[1]	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy
Started	118	123
Completed	40	45
Not completed	78	78
Consent withdrawn by subject	4	8
Death	44	42
Lost to follow-up	30	28

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: Only participants who consented for follow-up were included in this period.

Baseline characteristics

Reporting groups	
Reporting group title	Herceptin IV + Chemotherapy

Reporting group description:

Participants received eight cycles of Herceptin IV plus chemotherapy prior to surgery and ten cycles of Herceptin IV after surgery. Chemotherapy consisted of docetaxel 75 milligrams per meter-squared (mg/m^2) every 21 days for four cycles followed by 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2 (FEC) every 21 days for four cycles. Herceptin was administered as 8 milligrams per kilogram (mg/kg) on Day 1 and then as 6 mg/kg on Day 22 and every 21 days thereafter. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the Treatment-Free Follow-Up (TFFU) Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the Survival Follow-Up (SFU) Period.

Reporting group title	Herceptin SC + Chemotherapy

Reporting group description:

Participants received eight cycles of Herceptin SC plus chemotherapy prior to surgery and ten cycles of Herceptin SC after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as a 600-milligram (mg) fixed dose given every 21 days. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Reporting group values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy	Total
Number of subjects	299	297	596
Age Categorical Units: Subjects			
Age Continuous			
Analysis was performed on Intent-to-Treat (ITT) Population, which included participants with at least one efficacy assessment after administration of the first treatment cycle. (N=297, 294, respectively).			
Units: years			
arithmetic mean	49.5	50.3	
standard deviation	± 10.83	± 11.08	-
Gender Categorical Units: Subjects			
Female	299	297	596
Male	0	0	0

End points

End points reporting groups

Reporting group title	Herceptin IV + Chemotherapy

Reporting group description:

Participants received eight cycles of Herceptin IV plus chemotherapy prior to surgery and ten cycles of Herceptin IV after surgery. Chemotherapy consisted of docetaxel 75 milligrams per meter-squared (mg/m^2) every 21 days for four cycles followed by 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2 (FEC) every 21 days for four cycles. Herceptin was administered as 8 milligrams per kilogram (mg/kg) on Day 1 and then as 6 mg/kg on Day 22 and every 21 days thereafter. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the Treatment-Free Follow-Up (TFFU) Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the Survival Follow-Up (SFU) Period.

Reporting group title	Herceptin SC + Chemotherapy

Reporting group description:

Participants received eight cycles of Herceptin SC plus chemotherapy prior to surgery and ten cycles of Herceptin SC after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as a 600-milligram (mg) fixed dose given every 21 days. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Reporting group title	Herceptin IV + Chemotherapy

Reporting group description:

Participants received eight cycles of Herceptin IV plus chemotherapy prior to surgery and ten cycles of Herceptin IV after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as 8 mg/kg on Day 1 and then as 6 mg/kg on Day 22 and every 21 days thereafter. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Reporting group title	Herceptin SC + Chemotherapy

Reporting group description:

Participants received eight cycles of Herceptin SC plus chemotherapy prior to surgery and ten cycles of Herceptin SC after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as a 600-mg fixed dose given every 21 days. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Reporting group title	Herceptin IV + Chemotherapy

Reporting group description:

Participants received eight cycles of Herceptin IV plus chemotherapy prior to surgery and ten cycles of Herceptin IV after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as 8 mg/kg on Day 1 and then as 6 mg/kg on Day 22 and every 21 days thereafter. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Reporting group title	Herceptin SC + Chemotherapy

Reporting group description:

Participants received eight cycles of Herceptin SC plus chemotherapy prior to surgery and ten cycles of Herceptin SC after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four

cycles followed by FEC every 21 days for four cycles. Herceptin was administered as a 600-mg fixed dose given every 21 days. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Primary: Observed Serum Trough Concentration (Ctrough) of Trastuzumab Prior to Surgery

End point title	Observed Serum Trough Concentration (Ctrough) of Trastuzumab Prior to Surgery

End point description:

Pre-dose samples were obtained prior to surgery (Cycle 8). The observed Ctrough was recorded, averaged among all participants, and expressed in micrograms per milliliter (mcg/mL). Analysis was performed on Primary Pharmacokinetic (PK) Per Protocol (PP) Population, which included all participants with at least one measurable trastuzumab serum concentration and who did not have any major protocol violations related to PK sampling for the primary endpoint.

End point type	Primary

End point timeframe:

Pre-dose (0 hours) on Day 1 of Cycle 8 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	234		
Units: mcg/mL				
arithmetic mean (standard deviation)	57.8 (± 30.3)	78.7 (± 43.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

PK sample size calculations based on percentage of coefficient of variation (CV%) for Ctrough of trastuzumab from previous metastatic breast cancer (MBC) and early breast cancer (EBC) studies. Because pre-surgery situation was comparable to MBC setting, interpatient CV% of 60 percent (%) was assumed and 130 participants per arm (260 participants total) were needed to demonstrate Ctrough comparability with 80% power if the true means of the two formulations did not differ by greater than (>) 5%.

Comparison groups	Herceptin IV + Chemotherapy v Herceptin SC + Chemotherapy
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Geometric mean ratio
Point estimate	1.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.24
upper limit	1.44

Notes:

[1] - Non-inferiority was concluded if the lower limit of the 90% confidence interval (CI) was greater than or equal to (>/=) 0.8 for the geometric mean ratio (ratio of test treatment group [Herceptin SC + Chemotherapy] to reference treatment group [Herceptin IV + Chemotherapy]).

Primary: Percentage of Participants with Pathological Complete Response (pCR)

End point title	Percentage of Participants with Pathological Complete Response (pCR)

End point description:

Participants were evaluated following eight cycles of treatment and after surgery to assess for pCR, defined as absence of neoplastic invasive cells in the breast according to pathologist examination. The percentage of participants with pCR was reported, and the 95% CI for one-sample binomial was constructed using the Pearson-Clopper method. Analysis was performed on Efficacy (E) PP Population, which included all participants with at least one on-treatment efficacy assessment who received a full eight cycles of study treatment according to randomization and who met additional protocol-specified criteria.

End point type	Primary

End point timeframe:

After surgery following eight cycles of Herceptin + chemotherapy (approximately 6 months from Baseline)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	260		
Units: percentage of participants				
number (confidence interval 95%)	40.7 (34.7 to 46.9)	45.4 (39.2 to 51.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Assuming pCR rates of at least 40% in both arms, 552 participants were necessary to conclude non-inferiority in pCR rate with a power of 80% using a one-sided 97.5% CI for the difference of the response rates and a non-inferiority margin of 12.5%.

Comparison groups	Herceptin IV + Chemotherapy v Herceptin SC + Chemotherapy
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in response rates
Point estimate	4.7
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-4

Notes:

[2] - Non-inferiority was concluded if the lower limit of the one-sided 97.5% CI was above -12.5% for the difference in response (pCR) rates. The one-sided 97.5% CI for the difference in response (pCR) rates was calculated using the Anderson-Hauck continuity correction.

Secondary: Observed Ctrough of Trastuzumab After Surgery

End point title	Observed Ctrough of Trastuzumab After Surgery

End point description:

Pre-dose samples were obtained after surgery (Cycle 13). The observed Ctrough was recorded, averaged among all participants, and expressed in mcg/mL. Analysis was performed on Secondary PKPP Population, which included all participants with at least one measurable trastuzumab serum concentration and who did not have any major protocol violations related to PK sampling for the secondary endpoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) on Day 1 of Cycle 13 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	227		
Units: mcg/mL				
arithmetic mean (standard deviation)	62.1 (± 37.1)	90.4 (± 41.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Additional supportive analysis

Comparison groups	Herceptin IV + Chemotherapy v Herceptin SC + Chemotherapy
Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Geometric mean ratio
Point estimate	1.51
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.4
upper limit	1.63

Notes:

[3] - Geometric mean ratio = ratio of test treatment group (Herceptin SC + Chemotherapy) to reference treatment group (Herceptin IV + Chemotherapy)

Secondary: Predicted Ctrough of Trastuzumab Prior to Surgery

End point title	Predicted Ctrough of Trastuzumab Prior to Surgery

End point description:

Predicted Ctrough at pre-dose prior to surgery (Cycle 8) was determined on the basis of a population PK model from Study BP22023 (NCT00800436). The mean predicted Ctrough was expressed in mcg/mL. Analysis was performed on PKPP Population.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) on Day 1 of Cycle 8 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	278		
Units: mcg/mL				
arithmetic mean (standard deviation)	51.4 (± 19.4)	80.3 (± 33.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Additional supportive analysis.	
Comparison groups	Herceptin IV + Chemotherapy v Herceptin SC + Chemotherapy
Number of subjects included in analysis	554
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Geometric mean ratio
Point estimate	1.55
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.46
upper limit	1.64

Notes:

[4] - Geometric mean ratio = ratio of test treatment group (Herceptin SC + Chemotherapy) to reference treatment group (Herceptin IV + Chemotherapy).

Secondary: Predicted Ctrough of Trastuzumab After Surgery

End point title	Predicted Ctrough of Trastuzumab After Surgery

End point description:

Predicted Ctrough at pre-dose after surgery (Cycle 13) was determined on the basis of a population PK model from Study BP22023 (NCT00800436). The mean predicted Ctrough was expressed in mcg/mL. Analysis was performed on PKPP Population. Only participants with a Cycle 13 pre-dose PK measurement were included in the analysis.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) on Day 1 of Cycle 13 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	236		
Units: mcg/mL				
arithmetic mean (standard deviation)	51.7 (± 20.0)	80.6 (± 33.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Additional supportive analysis	
Comparison groups	Herceptin IV + Chemotherapy v Herceptin SC + Chemotherapy
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Geometric mean ratio
Point estimate	1.55
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.45
upper limit	1.64

Notes:

[5] - Geometric mean ratio = ratio of test treatment group (Herceptin SC + Chemotherapy) to reference treatment group (Herceptin IV + Chemotherapy).

Secondary: Number of Participants with Ctrough of Trastuzumab >20 mcg/mL Prior to Surgery

End point title	Number of Participants with Ctrough of Trastuzumab >20 mcg/mL Prior to Surgery

End point description:

Pre-dose samples were obtained prior to surgery (Cycle 8). The number of participants who had an observed Ctrough >20 mcg/mL was reported. Analysis was performed on primary PKPP Population.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) on Day 1 of Cycle 8 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	234		
Units: participants	232	227		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Ctrough of Trastuzumab >20 mcg/mL After Surgery

End point title	Number of Participants with Ctrough of Trastuzumab >20 mcg/mL After Surgery

End point description:

Pre-dose samples were obtained after surgery (Cycle 13). The number of participants who had an observed Ctrough >20 mcg/mL was reported. Analysis was performed on secondary PKPP population.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) on Day 1 of Cycle 13 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	227		
Units: participants	216	227		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of Trastuzumab Prior to Surgery

End point title	Maximum Serum Concentration (Cmax) of Trastuzumab Prior to Surgery

End point description:

PK samples were obtained prior to surgery (Cycle 7). The Cmax during Cycle 7 was recorded, averaged among all participants, and expressed in mcg/mL. Analysis was performed on Primary PKPP Population. Only those participants who provided evaluable data were included in the analysis.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) and at end of 30-minute infusion (Herceptin IV only) on Day 1 of Cycle 7; on Days 2, 4, 8, 15 of Cycle 7; pre-dose (0 hours) on Day 1 of Cycle 8 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	233		
Units: mcg/mL				
arithmetic mean (standard deviation)	221 (± 118)	149 (± 64.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Maximum Serum Concentration (Tmax) of Trastuzumab Prior to Surgery

End point title	Time of Maximum Serum Concentration (Tmax) of Trastuzumab Prior to Surgery

End point description:

PK samples were obtained prior to surgery (Cycle 7). The Tmax during Cycle 7 was recorded, averaged among all participants, and expressed in days. Analysis was performed on Primary PKPP Population. Only those participants who provided evaluable data were included in the analysis.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) and at end of 30-minute infusion (Herceptin IV only) on Day 1 of Cycle 7; on Days 2, 4, 8, 15 of Cycle 7; pre-dose (0 hours) on Day 1 of Cycle 8 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	233		
Units: days				
arithmetic mean (standard deviation)	0.05 (± 0.04)	4.12 (± 2.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve from 0 to 21 Days (AUC21d) of Trastuzumab Prior to Surgery

End point title	Area Under the Concentration-Time Curve from 0 to 21 Days (AUC21d) of Trastuzumab Prior to Surgery

End point description:

PK samples were obtained prior to surgery (Cycle 7). Values were extrapolated beyond Day 15 to produce the area over the full 21-day cycle. The AUC21d value at Cycle 7 was calculated from trastuzumab concentration-time profiles using standard non-compartmental PK methods, averaged among all participants, and expressed in days multiplied by micrograms per milliliter (d*mcg/mL). Analysis was performed on Primary PKPP Population. Only those participants who provided evaluable data were included in the analysis.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) and at end of 30-minute infusion (Herceptin IV only) on Day 1 of Cycle 7; on Days 2, 4, 8, 15 of Cycle 7; pre-dose (0 hours) on Day 1 of Cycle 8 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	233		
Units: d*mcg/mL				
arithmetic mean (standard deviation)	2056 (± 598)	2268 (± 875)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Trastuzumab After Surgery

End point title	Cmax of Trastuzumab After Surgery

End point description:

PK samples were obtained after surgery (Cycle 12). The Cmax during Cycle 12 was recorded, averaged among all participants, and expressed in mcg/mL. Analysis was performed on Secondary PKPP population. Only those participants who provided evaluable data were included in the analysis.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) and at end of 30-minute infusion (Herceptin IV only) on Day 1 of Cycle 12; on Days 2, 4, 8, 15 of Cycle 12; pre-dose (0 hours) on Day 1 of Cycle 13 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: mcg/mL				
arithmetic mean (standard deviation)	230 (± 118)	166 (± 58.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Trastuzumab After Surgery

End point title	Tmax of Trastuzumab After Surgery

End point description:

PK samples were obtained after surgery (Cycle 12). The Tmax during Cycle 12 was recorded, averaged among all participants, and expressed in days. Analysis was performed on Secondary PKPP population. Only those participants who provided evaluable data were included in the analysis.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) and at end of 30-minute infusion (Herceptin IV only) on Day 1 of Cycle 12; on Days 2, 4, 8, 15 of Cycle 12; pre-dose (0 hours) on Day 1 of Cycle 13 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	222		
Units: days				
arithmetic mean (standard deviation)	0.06 (± 0.13)	4.08 (± 2.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC21d of Trastuzumab After Surgery

End point title	AUC21d of Trastuzumab After Surgery

End point description:

PK samples were obtained after surgery (Cycle 12). Values were extrapolated beyond Day 15 to produce the area over the full 21-day cycle. The AUC21d value at Cycle 12 was calculated from trastuzumab concentration-time profiles using standard non-compartmental PK methods, averaged among all participants, and expressed in d*mcg/mL. Analysis was performed on Secondary PKPP population. Only those participants who provided evaluable data were included in the analysis.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours) and at end of 30-minute infusion (Herceptin IV only) on Day 1 of Cycle 12; on Days 2, 4, 8, 15 of Cycle 12; pre-dose (0 hours) on Day 1 of Cycle 13 (cycle length of 21 days)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: d*mcg/mL				
arithmetic mean (standard deviation)	2179 (± 725)	2610 (± 945)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Total Pathological Complete Response (tpCR)

End point title	Percentage of Participants with Total Pathological Complete Response (tpCR)

End point description:

Participants were evaluated following eight cycles of treatment and after surgery to assess for tpCR, defined as absence of neoplastic invasive cells in the breast and axillary lymph nodes according to pathologist examination. The percentage of participants with tpCR was reported, and the 95% CI for

one-sample binomial was constructed using the Pearson-Clopper method. Analysis was performed on EPP Population.

End point type	Secondary

End point timeframe:

After surgery following eight cycles of Herceptin + chemotherapy (approximately 6 months from Baseline)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	260		
Units: percentage of participants				
number (confidence interval 95%)	34.2 (28.5 to 40.3)	39.2 (33.3 to 45.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The 95% CI for the difference in response (tpCR) rates was calculated using the Anderson-Hauck continuity correction.

Comparison groups	Herceptin IV + Chemotherapy v Herceptin SC + Chemotherapy
Number of subjects included in analysis	523
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in response rates
Point estimate	5.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	13.5

Secondary: Percentage of Participants with Complete Response (CR) or Partial Response (PR) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0, Among Those with Measurable Disease at Baseline

End point title	Percentage of Participants with Complete Response (CR) or Partial Response (PR) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0, Among Those with Measurable Disease at Baseline

End point description:

Tumor response was assessed using RECIST version 1.0. CR was defined as disappearance of all target lesions and short axis reduction of any pathological lymph nodes to less than (<) 10 millimeters (mm) with no prior assessment of progressive disease (PD). PR was defined as greater than or equal to (>/=) 30% decrease from Baseline in sum diameter (SD) of target lesions with no prior assessment of PD. PD was defined as >/=20% relative increase and >/=5 mm of absolute increase in the SD of target lesions, taking as reference the smallest SD recorded since treatment started; or appearance of 1 or more new lesions. The percentage of participants with overall response of CR or PR at the end of neoadjuvant treatment was reported, and the 95% CI for one-sample binomial was constructed using the Pearson-

Clopper method. Analysis was performed on EPP Population. Only participants with measurable disease at Baseline were included.

End point type	Secondary

End point timeframe:

Tumor assessments at Baseline; on Day 1 of Cycles 3, 5, 7 (cycle length of 21 days); and at time of surgery following eight cycles of Herceptin + chemotherapy (approximately 6 months overall)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260	258		
Units: percentage of participants				
number (confidence interval 95%)	88.8 (84.4 to 92.4)	87.2 (82.5 to 91.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Odds Ratio (OR) = ratio of test treatment group (Herceptin SC + Chemotherapy) to reference treatment group (Herceptin IV + Chemotherapy).

Comparison groups	Herceptin IV + Chemotherapy v Herceptin SC + Chemotherapy
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.46

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The 95% CI for the difference in response (CR+PR) rates was calculated using the Anderson-Hauck continuity correction.

Comparison groups	Herceptin IV + Chemotherapy v Herceptin SC + Chemotherapy
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in response rates
Point estimate	-1.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	4.2

Secondary: Time to Response According to RECIST Version 1.0, Among Those with Measurable Disease at Baseline

End point title	Time to Response According to RECIST Version 1.0, Among Those with Measurable Disease at Baseline

End point description:

Tumor response was assessed using RECIST version 1.0. CR was defined as disappearance of all target lesions and short-axis reduction of any pathological lymph nodes to <10 mm with no prior assessment of PD. PR was defined as >/=30% decrease from Baseline in SD of target lesions with no prior assessment of PD. PD was defined as >/=20% relative increase and >/=5 mm of absolute increase in the SD of target lesions, taking as reference the smallest SD recorded since treatment started; or appearance of 1 or more new lesions. Time to response was defined as the time from first dose of study medication to the first assessment of CR or PR, which was the date the response was first documented by objective evidence, among participants with an overall response of CR or PR. Analysis was performed on EPP Population. Only participants with measurable disease at Baseline and a response of CR or PR were included.

End point type	Secondary

End point timeframe:

Tumor assessments at Baseline; on Day 1 Cycles 3, 5, 7 (cycle length of 21 days); and at time of surgery following eight cycles of chemotherapy (approximately 6 months overall)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	225		
Units: weeks				
median (full range (min-max))	6.14 (3 to 25)	6.14 (3 to 28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced a Protocol-Defined Event

End point title	Percentage of Participants Who Experienced a Protocol-Defined Event

End point description:

Protocol-defined events included disease recurrence/progression (local, regional, distant, contralateral) or death from any cause. Imaging was performed at specified visits for up to 5 years after last dose. Thereafter, participants were followed for survival only. The percentage of participants who experienced a protocol-defined event at any time during the study was reported. Analysis was performed on ITT Population.

End point type	Secondary

End point timeframe:

Screening; Day 1 of Cycle 18 (cycle length of 21 days); and Months 6, 12, 24, 36, 48, 60 from last dose

of Cycle 18; then
every 6 months until withdrawal for any reason (up to approximately 87 months overall)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	294		
Units: percentage of participants				
number (not applicable)	33.3	32.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)

End point description:

Protocol-defined events included disease recurrence or progression (local, regional, distant, contralateral) or death from any cause. Imaging was performed at specified visits for up to 5 years after last dose. Thereafter, participants were followed for survival only. EFS was estimated by Kaplan-Meier analysis and defined as the time from randomization to the first protocol-defined event. Analysis was performed on ITT Population. The value "9.9999" in results indicate that median time to event could not be determined because of a high number (>50%) of censored observations. Full range includes censored observations.

End point type	Secondary

End point timeframe:

Screening; Day 1 of Cycle 18 (cycle length of 21 days); and Months 6, 12, 24, 36, 48, 60 from last dose of Cycle 18; then every 6 months until withdrawal for any reason (up to approximately 87 months overall)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	294		
Units: months				
median (full range (min-max))	9.9999 (1 to 82)	9.9999 (1 to 76)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard Ratio (HR): ratio of test treatment group (Herceptin SC + Chemotherapy) to reference treatment group (Herceptin IV + Chemotherapy)

Comparison groups	Herceptin IV + Chemotherapy v Herceptin SC + Chemotherapy

Number of subjects included in analysis	591
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8651
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.29

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

The percentage of participants who died at any time during the study was reported. Analysis was performed on ITT Population.

End point type	Secondary

End point timeframe:

Continuously during treatment (up to 12 months); at Months 1, 3, 6 from last dose of Cycle 18 (cycle length of 21 days); then every 6 months until withdrawal for any reason (up to approximately 87 months overall)

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	294		
Units: percentage of participants				
number (not applicable)	14.5	13.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was estimated by Kaplan-Meier analysis and defined as the time from randomization to death from any cause. Analysis was performed on ITT Population. The value "9.9999" in results indicate that median OS could not be determined because of a high number (>50%) of censored observations. Full range includes censored observations.

End point type	Secondary

End point timeframe:

Continuously during treatment (up to 12 months); at Months 1, 3, 6 from last dose of Cycle 18 (cycle length of 21 days); then every 6 months until withdrawal for any reason (up to approximately 87

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	294		
Units: months				
median (full range (min-max))	9.9999 (2 to 82)	9.9999 (3 to 79)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard Ratio (HR): ratio of test treatment group (Herceptin SC + Chemotherapy) to reference treatment group (Herceptin IV + Chemotherapy)

Comparison groups	Herceptin IV + Chemotherapy v Herceptin SC + Chemotherapy
Number of subjects included in analysis	591
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7767
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.45

Secondary: Number of Participants with Anti-Drug Antibodies (ADAs) Against Trastuzumab

End point title	Number of Participants with Anti-Drug Antibodies (ADAs) Against Trastuzumab

End point description:

Participants provided PK samples for evaluation of anti-trastuzumab antibodies. The number of participants with "Treatment-induced ADAs" and "Treatment-enhanced ADA" against trastuzumab at any time during or after treatment was reported. Treatment-induced ADA = a participant with negative or missing Baseline ADA result(s) and at least one positive post-Baseline ADA result. Treatment-enhanced ADA = a participant with positive ADA result at Baseline who has one or more post Baseline titer results that are at least 0.60 titer unit greater than the Baseline titer result (four-fold increase of titer). Analysis was performed on Safety Population, which included all participants who received at least one dose of study medication. Here, Number of Subjects Analysed = participants who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline; pre-dose (0 hours) on Day 1 of Cycles 2, 5, 13, 18 (cycle length of 21 days); and Months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60 from last dose of Cycle 18

End point values	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	296	295		
Units: participants				
Treatment-induced ADAs	28	46		
Treatment-enhanced ADA	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with ADAs Against Recombinant Human Hyaluronidase (rHuPH20)

End point title	Number of Participants with ADAs Against Recombinant Human Hyaluronidase (rHuPH20)[6]

End point description:

Participants in the Herceptin SC arm provided PK samples for evaluation of anti-rHuPH20 antibodies. The number of participants with "Treatment-induced ADAs" and "Treatment-enhanced ADA" against rHuPH20 (an excipient unique to the SC formulation) at any time during or after treatment was reported. Treatment-induced ADA = a participant with negative or missing Baseline ADA result(s) and at least one positive post-Baseline ADA result. Treatment-enhanced ADA = a participant with positive ADA result at Baseline who has one or more post Baseline titer results that are at least 0.60 titer unit greater than the Baseline titer result (four-fold increase of titer). Analysis was performed on Safety Population. Here, Number of Subjects Analysed = participants who were evaluable for this outcome measure. As rHuPH20 is unique to SC formulation, this outcome measure was applicable for "Herceptin SC + Chemotherapy" arm only.

End point type	Secondary

End point timeframe:

Baseline; pre-dose (0 hours) on Day 1 of Cycles 2, 5, 13, 18 (cycle length of 21 days); and Months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60 from last dose of Cycle 18

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Reported analysis was planned to be carried out in the indicated arm only.

End point values	Herceptin SC + Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	295			
Units: participants				
Treatment-induced ADA	49			
Treatment-enhanced ADA	13			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 87 months overall

Adverse event reporting additional description:

Analysis was performed on Safety Population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Herceptin IV + Chemotherapy

Reporting group description:

Participants received eight cycles of Herceptin IV plus chemotherapy prior to surgery and ten cycles of Herceptin IV after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as 8 mg/kg on Day 1 and then as 6 mg/kg on Day 22 and every 21 days thereafter. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Reporting group title	Herceptin SC + Chemotherapy

Reporting group description:

Participants received eight cycles of Herceptin SC plus chemotherapy prior to surgery and ten cycles of Herceptin SC after surgery. Chemotherapy consisted of docetaxel 75 mg/m^2 every 21 days for four cycles followed by FEC every 21 days for four cycles. Herceptin was administered as a 600-mg fixed dose given every 21 days. The first eight cycles prior to surgery comprised the Neoadjuvant Treatment Period, and the ten cycles of Herceptin IV after surgery comprised the Adjuvant Treatment Period. Thereafter, participants entered the TFFU Period. Participants who were withdrawn from the Neoadjuvant Treatment Period for any reason, or who experienced disease recurrence during either the Adjuvant Treatment Period or TFFU Period, could be entered into the SFU Period.

Serious adverse events	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 298 (15.10%)	65 / 297 (21.89%)	
number of deaths (all causes)	43	42	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	0 / 298 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myeloid leukaemia			

subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 298 (0.34%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphorrhoea			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
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			
Death			

subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 298 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 298 (0.67%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian haemorrhage			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian mass			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vaginal prolapse			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 298 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 298 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Ejection fraction			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour marker increased			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haematoma			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary radiation injury			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radius fracture			
subjects affected / exposed	1 / 298 (0.34%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 298 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 298 (0.34%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	10 / 298 (3.36%)	13 / 297 (4.38%)	
occurrences causally related to treatment / all	10 / 10	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	9 / 298 (3.02%)	7 / 297 (2.36%)	
occurrences causally related to treatment / all	11 / 11	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhoids			
subjects affected / exposed	1 / 298 (0.34%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 298 (0.34%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			

subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 298 (0.34%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 298 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis viral			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 298 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 298 (0.34%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			

subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 298 (1.34%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 298 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sepsis			

subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis bacterial			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 298 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 298 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 298 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Herceptin IV + Chemotherapy	Herceptin SC + Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	277 / 298 (92.95%)	283 / 297 (95.29%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	31 / 298 (10.40%)	30 / 297 (10.10%)	
occurrences (all)	40	34	
Hypertension			
subjects affected / exposed	14 / 298 (4.70%)	24 / 297 (8.08%)	
occurrences (all)	14	33	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	75 / 298 (25.17%)	75 / 297 (25.25%)	
occurrences (all)	150	137	
Fatigue			
subjects affected / exposed	80 / 298 (26.85%)	70 / 297 (23.57%)	
occurrences (all)	179	158	
Mucosal inflammation			
subjects affected / exposed	39 / 298 (13.09%)	31 / 297 (10.44%)	
occurrences (all)	64	41	
Pyrexia			
subjects affected / exposed	35 / 298 (11.74%)	35 / 297 (11.78%)	
occurrences (all)	41	52	
Pain			
subjects affected / exposed	15 / 298 (5.03%)	12 / 297 (4.04%)	
occurrences (all)	19	13	
Oedema peripheral			
subjects affected / exposed	30 / 298 (10.07%)	23 / 297 (7.74%)	
occurrences (all)	44	25	
Injection site pain			
subjects affected / exposed	0 / 298 (0.00%)	18 / 297 (6.06%)	
occurrences (all)	0	49	
Oedema			
subjects affected / exposed	15 / 298 (5.03%)	10 / 297 (3.37%)	
occurrences (all)	15	11	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	10 / 298 (3.36%)	15 / 297 (5.05%)	
occurrences (all)	10	15	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 298 (8.05%)	35 / 297 (11.78%)	
occurrences (all)	27	41	
Oropharyngeal pain			
subjects affected / exposed	19 / 298 (6.38%)	19 / 297 (6.40%)	
occurrences (all)	20	24	
Dyspnoea			

subjects affected / exposed	22 / 298 (7.38%)	21 / 297 (7.07%)	
occurrences (all)	25	28	
Epistaxis			
subjects affected / exposed	18 / 298 (6.04%)	19 / 297 (6.40%)	
occurrences (all)	23	21	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	31 / 298 (10.40%)	26 / 297 (8.75%)	
occurrences (all)	35	30	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	19 / 298 (6.38%)	16 / 297 (5.39%)	
occurrences (all)	22	23	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	34 / 298 (11.41%)	41 / 297 (13.80%)	
occurrences (all)	34	42	
Incision site pain			
subjects affected / exposed	24 / 298 (8.05%)	33 / 297 (11.11%)	
occurrences (all)	26	35	
Procedural pain			
subjects affected / exposed	16 / 298 (5.37%)	18 / 297 (6.06%)	
occurrences (all)	17	19	
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 298 (14.77%)	50 / 297 (16.84%)	
occurrences (all)	72	69	
Peripheral sensory neuropathy			
subjects affected / exposed	27 / 298 (9.06%)	33 / 297 (11.11%)	
occurrences (all)	30	34	
Dizziness			
subjects affected / exposed	28 / 298 (9.40%)	29 / 297 (9.76%)	
occurrences (all)	36	38	
Neuropathy peripheral			
subjects affected / exposed	18 / 298 (6.04%)	24 / 297 (8.08%)	
occurrences (all)	18	25	

Dysgeusia			
subjects affected / exposed	22 / 298 (7.38%)	24 / 297 (8.08%)	
occurrences (all)	39	38	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	135 / 298 (45.30%)	128 / 297 (43.10%)	
occurrences (all)	302	269	
Anaemia			
subjects affected / exposed	41 / 298 (13.76%)	34 / 297 (11.45%)	
occurrences (all)	49	43	
Leukopenia			
subjects affected / exposed	46 / 298 (15.44%)	30 / 297 (10.10%)	
occurrences (all)	105	52	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	109 / 298 (36.58%)	101 / 297 (34.01%)	
occurrences (all)	189	178	
Nausea			
subjects affected / exposed	147 / 298 (49.33%)	145 / 297 (48.82%)	
occurrences (all)	316	290	
Vomiting			
subjects affected / exposed	69 / 298 (23.15%)	69 / 297 (23.23%)	
occurrences (all)	108	114	
Stomatitis			
subjects affected / exposed	51 / 298 (17.11%)	57 / 297 (19.19%)	
occurrences (all)	70	96	
Constipation			
subjects affected / exposed	45 / 298 (15.10%)	43 / 297 (14.48%)	
occurrences (all)	74	59	
Dyspepsia			
subjects affected / exposed	30 / 298 (10.07%)	33 / 297 (11.11%)	
occurrences (all)	44	44	
Abdominal pain upper			
subjects affected / exposed	27 / 298 (9.06%)	21 / 297 (7.07%)	
occurrences (all)	37	31	
Abdominal pain			

subjects affected / exposed	16 / 298 (5.37%)	22 / 297 (7.41%)	
occurrences (all)	20	32	
Skin and subcutaneous tissue disorders			
Nail disorder			
subjects affected / exposed	31 / 298 (10.40%)	29 / 297 (9.76%)	
occurrences (all)	31	29	
Alopecia			
subjects affected / exposed	188 / 298 (63.09%)	187 / 297 (62.96%)	
occurrences (all)	193	192	
Pruritus			
subjects affected / exposed	27 / 298 (9.06%)	26 / 297 (8.75%)	
occurrences (all)	31	30	
Skin hyperpigmentation			
subjects affected / exposed	24 / 298 (8.05%)	20 / 297 (6.73%)	
occurrences (all)	25	36	
Palmar−plantar erythrodysaesthesia syndrome			
subjects affected / exposed	18 / 298 (6.04%)	20 / 297 (6.73%)	
occurrences (all)	19	25	
Erythema			
subjects affected / exposed	8 / 298 (2.68%)	21 / 297 (7.07%)	
occurrences (all)	8	25	
Dermatitis			
subjects affected / exposed	15 / 298 (5.03%)	14 / 297 (4.71%)	
occurrences (all)	24	14	
Rash			
subjects affected / exposed	44 / 298 (14.77%)	48 / 297 (16.16%)	
occurrences (all)	68	74	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	54 / 298 (18.12%)	61 / 297 (20.54%)	
occurrences (all)	96	109	
Arthralgia			
subjects affected / exposed	60 / 298 (20.13%)	53 / 297 (17.85%)	
occurrences (all)	91	86	
Pain in extremity			

subjects affected / exposed	26 / 298 (8.72%)	29 / 297 (9.76%)	
occurrences (all)	33	42	
Back pain			
subjects affected / exposed	25 / 298 (8.39%)	26 / 297 (8.75%)	
occurrences (all)	32	31	
Musculoskeletal pain			
subjects affected / exposed	22 / 298 (7.38%)	18 / 297 (6.06%)	
occurrences (all)	28	29	
Bone pain			
subjects affected / exposed	10 / 298 (3.36%)	19 / 297 (6.40%)	
occurrences (all)	10	24	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	40 / 298 (13.42%)	24 / 297 (8.08%)	
occurrences (all)	55	39	
Urinary tract infection			
subjects affected / exposed	22 / 298 (7.38%)	10 / 297 (3.37%)	
occurrences (all)	24	13	
Upper respiratory tract infection			
subjects affected / exposed	30 / 298 (10.07%)	30 / 297 (10.10%)	
occurrences (all)	44	37	
Pharyngitis			
subjects affected / exposed	11 / 298 (3.69%)	15 / 297 (5.05%)	
occurrences (all)	12	15	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	59 / 298 (19.80%)	58 / 297 (19.53%)	
occurrences (all)	95	98	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2009	Following the availability of PK modeling data from 58 participants treated with trastuzumab SC in study BP22023 (NCT00800436), the protocol was updated to change the body weight-adjusted SC dosing to a fixed SC dose; The lymph node status as a stratification factor was deleted; Anti-rHuPH20 analysis was included and blood sampling for antibody testing was extended to include the treatment phase; A secondary analysis was added for the number of participants exceeding the target trastuzumab trough serum concentration of 20 mcg/mL; The inclusion of participants with inflammatory breast cancer without a measurable primary tumor was allowed.
04 October 2012	Following Health Authority request the treatment-free follow-up phase was extended to 5 years (60 months) in order to continue collection of safety and efficacy data; All participants in survival would be followed until the end of the study; Follow up analyses for safety and efficacy were to be run once all participants had completed 24 months of treatment-free follow-up and at the end of the study; The need to perform a confirmatory left ventricular ejection fraction (LVEF) assessment after a significant LVEF drop was applied throughout the full course of the study; Luteinizing Hormone Releasing Hormone agonists were added to the permitted concomitant hormonal therapy; In order to be consistent with requirements for the June 2011 update of the EU guideline, the timeline for serious adverse events reporting was changed from “one working day” to “within 24 hours”.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported