Clinical trial results:
A Randomized, Multicenter, Open-Label Cross-Over Study to Evaluate Patient Preference and Satisfaction of Subcutaneous Administration of the Fixed-Dose Combination of Pertuzumab and Trastuzumab in Patients with HER2-Positive Early Breast Cancer

Summary

EudraCT number	2018-002153-30
Trial protocol	ES PT SE FI
Global end of trial date	12 October 2022

Results information

Result version number	v3 (current)
This version publication date	30 December 2023
First version publication date	04 March 2021
Version creation reason	• Correction of full data set Corrections were made in order to align with the ClinicalTrials.gov results posting.

Trial information

Trial identification

Sponsor protocol code	MO40628

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03674112
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche, Ltd.
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study is to evaluate patient preference for pertuzumab and trastuzumab FDC SC.

Protection of trial subjects:

This study is conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. All participants are required to read and sign an informed consent form prior to participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 December 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Hong Kong: 8
Country: Number of subjects enrolled	Jordan: 5
Country: Number of subjects enrolled	Lebanon: 3
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Panama: 7
Country: Number of subjects enrolled	Portugal: 24
Country: Number of subjects enrolled	Qatar: 2
Country: Number of subjects enrolled	Saudi Arabia: 2
Country: Number of subjects enrolled	Serbia: 22
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United States: 23

Worldwide total number of subjects	160
EEA total number of subjects	58

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)	140
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 183 patients were screened and 160 participants were enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	A: P+H IV Followed by PH FDC SC

Arm description:

In the Treatment Cross-Over Period of the study, participants randomized to Arm A first received pertuzumab IV and trastuzumab IV (P+H IV) administration for 3 treatment cycles followed by the pertuzumab and trastuzumab fixed-dose combination subcutaneous (PH FDC SC) administration for 3 treatment cycles (1 cycle = 21 days). Following completion of this study period, participants chose one of the two study treatments to receive in the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment). After completing study treatment, participants entered the Follow-up Period wherein they were to be followed for 3 years from the date the last participant was randomized.

Arm type	Experimental
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	Perjeta
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab was non-weight based and was administered as an intravenous (IV) infusion once every 3 weeks (Q3W) in 2 dose configurations as follows: Loading dose of 840 milligrams (mg) IV, and maintenance dose of 420 mg IV. The dose and schedule were consistent with the prescribing information. Loading doses of pertuzumab and trastuzumab (P+H) IV were only required for subjects who had ≥6 weeks since their last neoadjuvant dose of P+H at study entry or ≥6 weeks since their last study treatment during the study. Maintenance doses were used for subsequent administrations or dose delays <6 weeks between doses.

Investigational medicinal product name	Pertuzumab and trastuzumab FDC SC
Investigational medicinal product code	RO7198574
Other name	Phesgo
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The pertuzumab and trastuzumab fixed-dose combination subcutaneous (FDC SC) administration was non-weight based and was administered as an SC injection to the thigh Q3W in 2 dose configurations as follows: Loading dose of 1200 milligrams (mg) pertuzumab and 600 mg trastuzumab SC; and maintenance dose of 600 mg pertuzumab and 600 mg trastuzumab SC. Loading doses of pertuzumab and trastuzumab (PH) FDC SC were only required for subjects who had ≥6 weeks since their last neoadjuvant dose of P+H at study entry or ≥6 weeks since their last study treatment during the study. Maintenance doses were used for subsequent administrations or dose delays <6 weeks between doses.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	Ro 45-2317
Other name	Herceptin

Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was weight based and was administered as an intravenous (IV) infusion Q3W after completion of the pertuzumab infusion and observation period in 2 dose configurations as follows: Loading dose of 8 milligrams per kilogram (mg/kg) IV, and maintenance dose of 6 mg/kg IV. The dose and schedule were consistent with the prescribing information. Loading doses of pertuzumab and trastuzumab (P+H) IV were only required for subjects who had ≥6 weeks since their last neoadjuvant dose of P+H at study entry or ≥6 weeks since their last study treatment during the study. Maintenance doses were used for subsequent administrations or dose delays <6 weeks between doses.

Arm title	B: PH FDC SC Followed by P+H IV

Arm description:

In the Treatment Cross-Over Period of the study, participants randomized to Arm B first received the pertuzumab and trastuzumab fixed-dose combination subcutaneous (PH FDC SC) administration for 3 treatment cycles followed by pertuzumab intravenous (IV) and trastuzumab IV (P+H IV) administration for 3 treatment cycles (1 cycle = 21 days). Following completion of this study period, participants chose one of the two study treatments to receive in the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment). After completing study treatment, participants entered the Follow-up Period wherein they were to be followed for 3 years from the date the last participant was randomized.

Arm type	Experimental
Investigational medicinal product name	Pertuzumab and trastuzumab FDC SC
Investigational medicinal product code	RO7198574
Other name	Phesgo
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The pertuzumab and trastuzumab fixed-dose combination subcutaneous (FDC SC) administration was non-weight based and was administered as an SC injection to the thigh Q3W in 2 dose configurations as follows: Loading dose of 1200 milligrams (mg) pertuzumab and 600 mg trastuzumab SC; and maintenance dose of 600 mg pertuzumab and 600 mg trastuzumab SC. Loading doses of pertuzumab and trastuzumab (PH) FDC SC were only required for subjects who had ≥6 weeks since their last neoadjuvant dose of P+H at study entry or ≥6 weeks since their last study treatment during the study. Maintenance doses were used for subsequent administrations or dose delays <6 weeks between doses.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	Ro 45-2317
Other name	Herceptin
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was weight based and was administered as an intravenous (IV) infusion Q3W after completion of the pertuzumab infusion and observation period in 2 dose configurations as follows: Loading dose of 8 milligrams per kilogram (mg/kg) IV, and maintenance dose of 6 mg/kg IV. The dose and schedule were consistent with the prescribing information. Loading doses of pertuzumab and trastuzumab (P+H) IV were only required for subjects who had ≥6 weeks since their last neoadjuvant dose of P+H at study entry or ≥6 weeks since their last study treatment during the study. Maintenance doses were used for subsequent administrations or dose delays <6 weeks between doses.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	Perjeta
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab was non-weight based and was administered as an intravenous (IV) infusion once every 3 weeks (Q3W) in 2 dose configurations as follows: Loading dose of 840 milligrams (mg) IV, and maintenance dose of 420 mg IV. The dose and schedule were consistent with the prescribing information. Loading doses of pertuzumab and trastuzumab (P+H) IV were only required for subjects who had ≥6 weeks since their last neoadjuvant dose of P+H at study entry or ≥6 weeks since their last study treatment during the study. Maintenance doses were used for subsequent administrations or dose delays <6 weeks between doses.

Number of subjects in period 1	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV
Started	80	80
Completed Cross-Over Treatment (C1-6)	80	80
Completed Cross-Over Period	79	80
Started Treatment Continuation	79	80
PH FDC SC for Treatment Continuation	70 [1]	68 [2]
P+H IV for Treatment Continuation	9 [3]	12 [4]
Completed Continuation Treatment (C7-18)	78	77
Completed Treatment Continuation Period	78	77
Started Follow-Up Period	80	79
Completed Follow-Up Period (≥3 Years)	73	75
Completed	73	75
Not completed	7	5
Consent withdrawn by subject	2	3
Death	2	-
Reason Not Specified	1	1
Lost to follow-up	2	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This study milestone "PH FDC SC for Treatment Continuation" indicates the number of participants randomized to Arm A for the Cross-Over Treatment Period who subsequently chose and received treatment with PH FDC SC during the Treatment Continuation Period.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This study milestone "PH FDC SC for Treatment Continuation" indicates the number of participants randomized to Arm B for the Cross-Over Treatment Period who subsequently chose and received treatment with PH FDC SC during the Treatment Continuation Period.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This study milestone "P+H IV for Treatment Continuation" indicates the number of participants randomized to Arm A for the Cross-Over Treatment Period who subsequently chose and received treatment with P+H IV during the Treatment Continuation Period.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This study milestone "P+H IV for Treatment Continuation" indicates the number of participants randomized to Arm B for the Cross-Over Treatment Period who subsequently chose and received treatment with P+H IV during the Treatment Continuation Period.

Baseline characteristics

Reporting groups	
Reporting group title	A: P+H IV Followed by PH FDC SC

Reporting group description:

In the Treatment Cross-Over Period of the study, participants randomized to Arm A first received pertuzumab IV and trastuzumab IV (P+H IV) administration for 3 treatment cycles followed by the pertuzumab and trastuzumab fixed-dose combination subcutaneous (PH FDC SC) administration for 3 treatment cycles (1 cycle = 21 days). Following completion of this study period, participants chose one of the two study treatments to receive in the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment). After completing study treatment, participants entered the Follow-up Period wherein they were to be followed for 3 years from the date the last participant was randomized.

Reporting group title	B: PH FDC SC Followed by P+H IV

Reporting group description:

In the Treatment Cross-Over Period of the study, participants randomized to Arm B first received the pertuzumab and trastuzumab fixed-dose combination subcutaneous (PH FDC SC) administration for 3 treatment cycles followed by pertuzumab intravenous (IV) and trastuzumab IV (P+H IV) administration for 3 treatment cycles (1 cycle = 21 days). Following completion of this study period, participants chose one of the two study treatments to receive in the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment). After completing study treatment, participants entered the Follow-up Period wherein they were to be followed for 3 years from the date the last participant was randomized.

Reporting group values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	Total
Number of subjects	80	80	160
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	68	72	140
From 65-84 years	12	8	20
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	49.4	48.2	
standard deviation	± 11.6	± 12.1	-
Sex: Female, Male			
Units: Participants			
Female	80	80	160
Male	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	17	21	38
Not Hispanic or Latino	59	54	113
Unknown or Not Reported	4	5	9
Race (NIH/OMB)			

Units: Subjects			
American Indian or Alaska Native	5	3	8
Asian	8	4	12
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	4
White	62	67	129
More than one race	0	0	0
Unknown or Not Reported	3	4	7
Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline			
ECOG Performance Status: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work.			
Units: Subjects			
ECOG Peformance Status 0	70	70	140
ECOG Peformance Status 1	10	10	20
Number of Cycles of Prior Neoadjuvant Pertuzumab IV and Trastuzumab IV Units: Subjects			
<4 Cycles	5	10	15
≥4 Cycles	75	70	145
Prior Neoadjuvant Chemotherapy Regimen			
Participants were stratified at randomization according to prior neoadjuvant chemotherapy regimen, pathological complete response to prior neoadjuvant treatment, and hormone receptor status.			
Units: Subjects			
Anthracyclines + Taxanes	55	53	108
Carboplatin + Taxanes	22	23	45
Taxanes Only	3	4	7
Pathological Complete Response (pCR) to Prior Neoadjuvant Treatment			
Participants were stratified at randomization according to prior neoadjuvant chemotherapy regimen, pathological complete response to prior neoadjuvant treatment, and hormone receptor status.			
Units: Subjects			
pCR	52	50	102
Non-pCR	28	30	58
Hormone Receptor Status			
Participants were stratified at randomization according to prior neoadjuvant chemotherapy regimen, pathological complete response to prior neoadjuvant treatment, and hormone receptor status (estrogen receptor [ER] and progesterone receptor [PgR]).			
Units: Subjects			
ER-Positive and/or PgR-Positive	53	51	104
ER-Negative and PgR-Negative	27	29	56
Baseline Weight Units: kilograms (kg)			
arithmetic mean	67.36	70.21	
standard deviation	± 12.08	± 14.15	-

End points reporting groups

Reporting group title	A: P+H IV Followed by PH FDC SC

Reporting group description:

In the Treatment Cross-Over Period of the study, participants randomized to Arm A first received pertuzumab IV and trastuzumab IV (P+H IV) administration for 3 treatment cycles followed by the pertuzumab and trastuzumab fixed-dose combination subcutaneous (PH FDC SC) administration for 3 treatment cycles (1 cycle = 21 days). Following completion of this study period, participants chose one of the two study treatments to receive in the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment). After completing study treatment, participants entered the Follow-up Period wherein they were to be followed for 3 years from the date the last participant was randomized.

Reporting group title	B: PH FDC SC Followed by P+H IV

Reporting group description:

In the Treatment Cross-Over Period of the study, participants randomized to Arm B first received the pertuzumab and trastuzumab fixed-dose combination subcutaneous (PH FDC SC) administration for 3 treatment cycles followed by pertuzumab intravenous (IV) and trastuzumab IV (P+H IV) administration for 3 treatment cycles (1 cycle = 21 days). Following completion of this study period, participants chose one of the two study treatments to receive in the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment). After completing study treatment, participants entered the Follow-up Period wherein they were to be followed for 3 years from the date the last participant was randomized.

Subject analysis set title	All Participants
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

In the Treatment Cross-Over Period of the study, all participants received their first 6 cycles of treatment in accordance with the study arm to which they were randomized: Arm A) pertuzumab IV and trastuzumab IV (P+H IV) for 3 treatment cycles followed by the pertuzumab and trastuzumab fixed-dose combination for subcutaneous administration (PH FDC SC) for 3 treatment cycles (1 cycle = 21 days); or Arm B) PH FDC SC for 3 treatment cycles followed by P+H IV for 3 treatment cycles (1 cycle = 21 days). Following completion of this study period, participants chose one of the two study treatments to receive in the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment). After completing study treatment, participants entered the Follow-up Period wherein they were to be followed for 3 years from the date the last participant was randomized.

Subject analysis set title	All Participants: TASQ-IV Completers
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This analysis set includes all participants from Arms A and B who completed the TASQ-IV questionnaire, which was administered at the last IV treatment cycle in the Treatment Cross-Over Period of the study. During the Treatment Cross-Over Period, all participants received their first 6 cycles of treatment in accordance with the study arm to which they were randomized: Arm A) pertuzumab IV and trastuzumab IV (P+H IV) for 3 treatment cycles followed by the pertuzumab and trastuzumab fixed-dose combination for subcutaneous administration (PH FDC SC) for 3 treatment cycles (1 cycle = 21 days); or Arm B) PH FDC SC for 3 treatment cycles followed by P+H IV for 3 treatment cycles (1 cycle = 21 days).

Subject analysis set title	All Participants: TASQ-SC Completers
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This analysis set includes all participants from Arms A and B who completed the TASQ-SC questionnaire, which was administered at the last SC treatment cycle in the Treatment Cross-Over Period of the study. During the Treatment Cross-Over Period, all participants received their first 6 cycles of treatment in accordance with the study arm to which they were randomized: Arm A) pertuzumab IV and trastuzumab IV (P+H IV) for 3 treatment cycles followed by the pertuzumab and trastuzumab fixed-dose combination for subcutaneous administration (PH FDC SC) for 3 treatment cycles (1 cycle = 21 days); or Arm B) PH FDC SC for 3 treatment cycles followed by P+H IV for 3 treatment cycles (1 cycle = 21 days).

Subject analysis set title	All Healthcare Professionals
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This analysis set includes all healthcare professionals who treated participants from Arms A and B and

completed the HCPQ questionnaire, which was administered at the last treatment cycle in the Treatment Cross-Over Period of the study. During the Treatment Cross-Over Period, all participants received their first 6 cycles of treatment in accordance with the study arm to which they were randomized: Arm A) pertuzumab IV and trastuzumab IV (P+H IV) for 3 treatment cycles followed by the pertuzumab and trastuzumab fixed-dose combination for subcutaneous administration (PH FDC SC) for 3 treatment cycles (1 cycle = 21 days); or Arm B) PH FDC SC for 3 treatment cycles followed by P+H IV for 3 treatment cycles (1 cycle = 21 days).

Subject analysis set title	Arm A: Treatment With P+H IV (Cycles 1–3)
Subject analysis set type	Safety analysis

Subject analysis set description:

This safety analysis population only includes the adverse events that occurred in Arm A participants during treatment Cycles 1 to 3 when all Arm A participants were treated with P+H IV. In the Treatment Cross-Over Period of the study, participants randomized to Arm A first received treatment with pertuzumab IV and trastuzumab IV (P+H IV) for 3 treatment cycles and that was followed by treatment with pertuzumab and trastuzumab FDC SC (PH FDC SC) for 3 treatment cycles (1 cycle = 21 days).

Subject analysis set title	Arm A: Treatment With PH FDC SC (Cycles 4–6)
Subject analysis set type	Safety analysis

Subject analysis set description:

This safety analysis population only includes adverse events that occurred in Arm A participants during treatment Cycles 4 to 6 when all Arm A participants were treated with PH FDC SC. In the Treatment Cross-Over Period of the study, participants randomized to Arm A first received treatment with pertuzumab IV and trastuzumab IV (P+H IV) for 3 treatment cycles and that was followed by treatment with pertuzumab and trastuzumab FDC SC (PH FDC SC) for 3 treatment cycles (1 cycle = 21 days).

Subject analysis set title	Arm B: Treatment With PH FDC SC (Cycles 1–3)
Subject analysis set type	Safety analysis

Subject analysis set description:

This safety analysis population only includes adverse events that occurred in Arm B participants during treatment Cycles 1 to 3 when all Arm B participants were treated with PH FDC SC. In the Treatment Cross-Over Period of the study, participants randomized to Arm B first received treatment with pertuzumab and trastuzumab FDC SC (PH FDC SC) for 3 treatment cycles and that was followed by treatment with pertuzumab IV and trastuzumab IV (P+H IV) for 3 treatment cycles (1 cycle = 21 days).

Subject analysis set title	Arm B: Treatment With P+H IV (Cycles 4–6)
Subject analysis set type	Safety analysis

Subject analysis set description:

This safety analysis population only includes adverse events that occurred in Arm B participants during treatment Cycles 4 to 6 when all Arm B participants were treated with P+H IV. In the Treatment Cross-Over Period of the study, participants randomized to Arm B first received treatment with pertuzumab and trastuzumab FDC SC (PH FDC SC) for 3 treatment cycles and that was followed by treatment with pertuzumab IV and trastuzumab IV (P+H IV) for 3 treatment cycles (1 cycle = 21 days).

Subject analysis set title	P+H IV: Treatment Cross-Over Period
Subject analysis set type	Safety analysis

Subject analysis set description:

This safety analysis population includes all participants from Arms A and B who received up to 3 cycles (1 cycle = 21 days) of treatment with pertuzumab IV and trastuzumab IV (P+H IV) during the Treatment Cross-Over Period of the study.

Subject analysis set title	PH FDC SC: Treatment Cross-Over Period
Subject analysis set type	Safety analysis

Subject analysis set description:

This safety analysis population includes all participants from Arms A and B who received up to 3 cycles (1 cycle = 21 days) of treatment with the pertuzumab and trastuzumab fixed-dose combination administered subcutaneously (PH FDC SC) during the Treatment Cross-Over Period of the study.

Subject analysis set title	P+H IV: Treatment Continuation Period
Subject analysis set type	Safety analysis

Subject analysis set description:

This safety analysis population includes all participants from Arms A and B who, following completion of the Treatment Cross-Over Period, chose to receive pertuzumab IV and trastuzumab IV (P+H IV) during the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment).

Subject analysis set title	PH FDC SC: Treatment Continuation Period
Subject analysis set type	Safety analysis

Subject analysis set description:

This safety analysis population includes all participants from Arms A and B who, following completion of the Treatment Cross-Over Period, chose to receive the pertuzumab and trastuzumab fixed-dose combination administered subcutaneously (PH FDC SC) during the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment).

Primary: Percentage of Participants by Their Preferred Method of Pertuzumab and Trastuzumab Administration, as Assessed in Question 1 of the Patient Preference Questionnaire (PPQ)

End point title	Percentage of Participants by Their Preferred Method of Pertuzumab and Trastuzumab Administration, as Assessed in Question 1 of the Patient Preference Questionnaire (PPQ)[1]

End point description:

Question 1 of the Patient Preference Questionnaire (PPQ) asked participants the following question: "All things considered, which method of administration did you prefer?" The three available options for a participant's response were: IV, SC, or No preference. A point estimate with associated exact Clopper-Pearson binomial 95% confidence interval (CI) was calculated only for the percentage of participants who preferred PH FDC SC (i.e., 95% CI values of 0.000000 to 999999 for IV and No Preference only indicate that they were not calculated). The modified Intent-to-Treat (mITT) population was analyzed, which included all randomized participants allocated to their randomized treatment arm, who received at least one dose by both SC and IV routes of administration during the Treatment Cross-over Period and subsequently answered at least Question 1 of the PPQ.

End point type	Primary

End point timeframe:

Cycle 6 Day 1 (each cycle is 21 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was planned for this study. The results are presented using descriptive statistics.

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	80	160	
Units: Percentage of participants				
number (confidence interval 95%)				
SC Preference	87.50 (78.21 to 93.84)	82.50 (72.38 to 90.09)	85.00 (78.51 to 90.15)	
IV Preference	12.5 (0.000000 to 999999)	15.0 (0.000000 to 999999)	13.8 (0.000000 to 999999)	
No Preference	0.0 (0.000000 to 999999)	2.5 (0.000000 to 999999)	1.3 (0.000000 to 999999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Responses to the Strength of Their Preferred Method of Pertuzumab and Trastuzumab Administration, as Assessed in Question 2 of the Patient Preference Questionnaire (PPQ)

End point title	Percentage of Participants by Responses to the Strength of Their Preferred Method of Pertuzumab and Trastuzumab Administration, as Assessed in Question 2 of the Patient

	Preference Questionnaire (PPQ)

End point description:

Question 1 of the Patient Preference Questionnaire (PPQ) was as follows: "All things considered, which method of administration did you prefer?" The available options for a participant's response were IV, SC, or No preference. In Question 2 of the PPQ, participants who reported a preference for one of the two administration routes in Question 1 of the PPQ were asked to rate the strength of their preference (very strong, fairly strong, not very strong). The modified ITT (mITT) Population was analyzed; for Question 2 of the PPQ, the number analyzed for the strength of SC or IV preference represents the participants who indicated in their responses to Question 1 of the PPQ that they preferred the SC or IV route of administration, respectively.

End point type	Secondary

End point timeframe:

Cycle 6 Day 1 (each cycle is 21 days)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	78	158	
Units: Percentage of participants				
number (not applicable)				
SC Preference: Very Strong (n=70,66,136)	68.6	66.7	67.6	
SC Preference: Fairly Strong (n=70,66,136)	24.3	25.8	25.0	
SC Preference: Not Very Strong (n=70,66,136)	7.1	7.6	7.4	
IV Preference: Very Strong (n=10,12,22)	40.0	66.7	54.5	
IV Preference: Fairly Strong (n=10,12,22)	10.0	8.3	9.1	
IV Preference: Not Very Strong (n=10,12,22)	50.0	25.0	36.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responses from Participants to the Two Main Reasons for Their Preferred Method of Pertuzumab and Trastuzumab Administration, as Assessed in Question 3 of the Patient Preference Questionnaire (PPQ)

End point title	Percentage of Responses from Participants to the Two Main Reasons for Their Preferred Method of Pertuzumab and Trastuzumab Administration, as Assessed in Question 3 of the Patient Preference Questionnaire (PPQ)

End point description:

In Question 3 of the PPQ, participants who reported a preference for one of the two administration routes in Question 1 of the PPQ were asked to provide the two main reasons for their preference. The five available options for a participant's response were: Feels less emotionally distressing; Requires less time in the clinic; Lower level of injection-site pain; Feels more comfortable during administration; and Other reason. The modified ITT (mITT) population was analyzed; for Question 3, the number analyzed for the two main reasons for SC or IV preference represents the participants who indicated in their responses to Question 1 of the PPQ that they preferred the SC or IV route of administration, respectively.

End point type	Secondary

End point timeframe:

Cycle 6 Day 1 (each cycle is 21 days)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	78	158	
Units: Percentage of responses				
number (not applicable)				
SC: Feels Less Emotionally Distressing	14.7	18.0	16.3	
SC: Requires Less Time in the Clinic	42.0	42.4	42.2	
SC: Lower Level of Injection-Site Pain	9.8	12.9	11.3	
SC: Feels More Comfortable During Administration	28.7	23.0	25.9	
SC: Other Reason	4.9	3.6	4.3	
IV: Feels Less Emotionally Distressing	17.6	16.0	16.7	
IV: Requires Less Time in the Clinic	5.9	4.0	4.8	
IV: Lower Level of Injection-Site Pain	23.5	28.0	26.2	
IV: Feels More Comfortable During Administration	47.1	24.0	33.3	
IV: Other Reason	5.9	28.0	19.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Their Level of Satisfaction with the Respective Methods of Administration (IV and SC), Question 1 of the Therapy Administration Satisfaction Questionnaire –Intravenous (TASQ-IV) and –Subcutaneous (TASQ-SC)

End point title	Percentage of Participants by Their Level of Satisfaction with the Respective Methods of Administration (IV and SC), Question 1 of the Therapy Administration Satisfaction Questionnaire –Intravenous (TASQ-IV) and –Subcutaneous (TASQ-SC)

End point description:

The Therapy Administration Satisfaction Questionnaire (TASQ) is a 12-item, patient-reported questionnaire measuring the impact of the mode of treatment administration (TASQ-IV for IV treatment and TASQ-SC for SC treatment) on five domains: Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction. The TASQ-IV/-SC was administered at treatment Cycles 3 and 6 according to the order of treatment received per arm during the Cross-Over Period. Question 1 of the TASQ-IV/TASQ-SC is one of two items in the Satisfaction domain, with participants providing their answers to the following question: "How satisfied or dissatisfied were you with the IV infusion/SC injection?" The five available options for a participant's response were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, and very dissatisfied. The modified Intent-to-Treat (mITT) population was analyzed.

End point type	Secondary

End point timeframe:

Cycle 3 Day 1, Cycle 6 Day 1 (each cycle is 21 days)

End point values	All Participants: TASQ-IV Completers	All Participants: TASQ-SC Completers		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160	160		
Units: Participants				
number (not applicable)				
Very Satisfied	25.6	57.5		
Satisfied	41.9	30.6		
Neither Satisfied nor Dissatisfied	25.6	4.4		
Dissatisfied	5.6	1.9		
Very Dissatisfied	1.3	4.4		
Did Not Answer Question	0.0	1.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Scores of the Five Domains of the TASQ-IV and TASQ-SC (Satisfaction, Physical Impact, Psychological Impact, Impact on Activities of Daily Living, and Convenience) to Assess the Impact of IV and SC Routes of Administration

End point title	Mean Scores of the Five Domains of the TASQ-IV and TASQ-SC (Satisfaction, Physical Impact, Psychological Impact, Impact on Activities of Daily Living, and Convenience) to Assess the Impact of IV and SC Routes of Administration

End point description:

The TASQ is a 12-item, patient-reported questionnaire measuring the impact of the mode of treatment administration (TASQ-IV for IV treatment and TASQ-SC for SC treatment) on 5 domains: Physical Impact (3 items: Question [Q]2. Pain, Q3. Swelling, Q4. Redness), Psychological Impact (1 item: Q5. Feeling restricted), Impact on Activities of Daily Living (1 item: Q8. Lost/gained time), Convenience (2 items: Q6. Is it convenient?, Q7. Bothered by the amount of time?), and Satisfaction (2 items: Q1. How satisfied or dissatisfied are you with treatment?, Q12: Would you recommend the way you received the treatment?). In addition, 3 questions in the TASQ (Q9, Q10, Q11) are not part of the domains. Responses for the 3 domains that contain more than 1 item were scored from 0 to 100, with a higher score indicating a better outcome. Responses for the 2 domains with 1 item were scored from 1 to 5, with a higher score indicating a better outcome.

End point type	Secondary

End point timeframe:

Cycle 3 Day 1, Cycle 6 Day 1 (each cycle is 21 days)

End point values	All Participants: TASQ-IV Completers	All Participants: TASQ-SC Completers		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160	160		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Satisfaction Domain	64.3 (± 23.6)	87.7 (± 17.5)		
Physical Impact Domain	86.5 (± 14.8)	81.3 (± 15.4)		
Psychological Impact Domain	3.8 (± 1.2)	4.6 (± 0.7)		
Impact on Activities Daily Living Domain	2.3 (± 0.9)	3.9 (± 1.0)		
Convenience Domain	56.8 (± 26.0)	90.0 (± 13.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Their Responses to Question 9 of the TASQ-IV and TASQ-SC, Assessing Whether Participants Receiving IV and SC Administration Have as Much Time as They Would Like to Talk to Their Nurse and/or Doctor About Their Illness

End point title	Percentage of Participants by Their Responses to Question 9 of the TASQ-IV and TASQ-SC, Assessing Whether Participants Receiving IV and SC Administration Have as Much Time as They Would Like to Talk to Their Nurse and/or Doctor About Their Illness

End point description:

The TASQ is a 12-item, patient-reported questionnaire measuring the impact of the mode of treatment administration (TASQ-IV for IV treatment and TASQ-SC for SC treatment) on 5 domains. In addition, 3 questions (Q.9-11) are not part of the domains. The TASQ-IV/-SC was administered at treatment Cycles 3 and 6 according to the order of treatment received per arm during the Cross-Over Period. Question 9 asked the participant, "When you receive the IV infusion/SC injection treatment, are you able to talk to your nurse and/or doctor as much as you would like about your illness?" There were five available response options: a) Yes, I had more than enough time to talk to my nurse and/or doctor; b) Yes, but I would have liked more time to talk to my nurse and/or doctor; c) It does not matter to me if I have time to talk to my nurse and/or doctor during my treatment; d) No, I did not have enough time to talk to my nurse and/or doctor; and e) No, I did not talk to my nurse and/or doctor at all.

End point type	Secondary

End point timeframe:

Cycle 3 Day 1 and Cycle 6 Day 1 (each cycle is 21 days)

End point values	All Participants: TASQ-IV Completers	All Participants: TASQ-SC Completers		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160	160		
Units: Percentage of participants				
number (not applicable)				
a) Yes, I had enough time to talk	82.5	90.0		

b) Yes, but I would have liked more time to talk	9.4	5.0		
c) It does not matter to me if I have time to talk	5.0	3.1		
d) No, I did not have enough time to talk	0.6	0.6		
e) No, I did not talk to my nurse/doctor	2.5	0.0		
Patient did not answer question	0.0	1.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Their Responses to Question 10 of the TASQ-IV and TASQ-SC, Assessing Whether IV and SC Administration Have an Impact on the Amount of Time Participants Have to Talk to Their Nurse and/or Doctor About Their Illness

End point title	Percentage of Participants by Their Responses to Question 10 of the TASQ-IV and TASQ-SC, Assessing Whether IV and SC Administration Have an Impact on the Amount of Time Participants Have to Talk to Their Nurse and/or Doctor About Their Illness

End point description:

The Therapy Administration Satisfaction Questionnaire (TASQ) is a 12-item, patient-reported questionnaire measuring the impact of the mode of treatment administration (TASQ-IV for IV treatment and TASQ-SC for SC treatment) on 5 domains (questions [Q] 1 to 8 and Q12): Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction. In addition, 3 questions in the TASQ-IV/-SC (Q 9-11) are not part of the domains. The TASQ-IV/-SC were administered at treatment Cycles 3 and 6 according to the order of treatment received in each study arm during the Cross-Over Period. Question 10 of the TASQ-IV/-SC asked the participant "Does the IV infusion/SC injection impact the amount of time you have to talk to your nurse and/or doctor about your illness and other concerns?" There were two available options for the participant's response: Yes or No.

End point type	Secondary

End point timeframe:

Cycle 3 Day 1 and Cycle 6 Day 1 (each cycle is 21 days)

End point values	All Participants: TASQ-IV Completers	All Participants: TASQ-SC Completers		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160	160		
Units: Percentage of participants				
number (not applicable)				
Yes	20.0	13.1		
No	79.4	85.0		
Patient Did Not Answer Question	0.6	1.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Their Responses to Question 11 of the TASQ-IV and TASQ-SC, Assessing the Participants' Preferred Method for Receiving Cancer Treatment

End point title	Percentage of Participants by Their Responses to Question 11 of the TASQ-IV and TASQ-SC, Assessing the Participants' Preferred Method for Receiving Cancer Treatment

End point description:

The Therapy Administration Satisfaction Questionnaire (TASQ) is a 12-item, patient-reported questionnaire measuring the impact of the mode of treatment administration (TASQ-IV for IV treatment and TASQ-SC for SC treatment) on 5 domains (questions [Q] 1 to 8 and Q12): Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction. In addition, 3 questions in the TASQ-IV/-SC (Q 9-11) are not part of the domains. The TASQ-IV/-SC was administered at treatment Cycles 3 and 6 according to the order of treatment received during the Cross-Over Period. Question 11 of the TASQ-IV/-SC asked the participant, "There are two ways to get cancer treatment: a) IV infusion given through a port or small tube; b) SC (subcutaneous) injection in your thigh. Which would you prefer?" There were three available options for the participant's response: IV, SC, or No Preference.

End point type	Secondary

End point timeframe:

Cycle 3 Day 1 and Cycle 6 Day 1 (each cycle is 21 days)

End point values	All Participants: TASQ-IV Completers	All Participants: TASQ-SC Completers		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	160	160		
Units: Percentage of participants				
number (not applicable)				
Prefer IV Method	11.9	9.4		
Prefer SC Method	70.6	82.5		
No Preference	11.9	5.6		
Patient Did Not Answer Question	5.6	2.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Their Choice of Treatment in the Treatment Continuation Period (PH FDC SC or P+H IV) and by Consistency of This Choice with Their Preferred Method of Administration Reported in Question 1 of the PPQ

End point title	Percentage of Participants by Their Choice of Treatment in the Treatment Continuation Period (PH FDC SC or P+H IV) and by Consistency of This Choice with Their Preferred Method of Administration Reported in Question 1 of the PPQ

End point description:

At treatment Cycle 6, Day 1, participants were expected to select the study treatment formulation (PH FDC SC or P+H IV) they would receive during the Treatment Continuation Period (starting at Cycle 7) to complete their 18 cycles of neo/adjuvant HER2-targeted treatment. Additionally, for each participant’s

preference category (SC, IV, and No preference) as per the question 1 of the patient preference questionnaire (PPQ), the percentage of participants who selected each treatment administration route for the Treatment Continuation Period (PH FDC SC or P+H IV) was summarized.

End point type	Secondary

End point timeframe:

Cycle 6 Day 1 (each cycle is 21 days)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	80	160	
Units: Percentage of participants				
number (not applicable)				
Chose SC for Treatment Continuation	88.8	85.0	86.9	
Chose IV for Treatment Continuation	11.3	15.0	13.1	
Preferred SC per PPQ & Chose SC for Continuation	87.5	82.5	85.0	
Preferred SC per PPQ & Chose IV for Continuation	0.0	0.0	0.0	
Preferred IV per PPQ & Chose SC for Continuation	1.3	0.0	0.6	
Preferred IV per PPQ & Chose IV for Continuation	11.3	15.0	13.1	
No Preference per PPQ & Chose SC for Continuation	0.0	2.5	1.3	
No Preference per PPQ & Chose IV for Continuation	0.0	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Treatment Administration Activities According to Healthcare Professionals' Responses on Perception of Time by Treatment Cycle, Question 1 of the Healthcare Professional Questionnaire (HCPQ) - Treatment Room

End point title	Duration of Treatment Administration Activities According to Healthcare Professionals' Responses on Perception of Time by Treatment Cycle, Question 1 of the Healthcare Professional Questionnaire (HCPQ) - Treatment Room

End point description:

The Healthcare Professional Questionnaire (HCPQ)-Treatment Room Question 1 was completed at each treatment cycle of the Treatment Cross-Over Period by the healthcare professionals (HCPs) who administered treatment to the study's participants. HCPs responded to the following parts of Question 1 that sought to evaluate the amount of time it took to complete activities related to treatment administration: "If new IV access was needed for this cycle of treatment, please indicate what type of IV access was provided (central venous catheter [CVC], peripherally inserted central catheter [PICC], or peripheral vein cannulation [PVC]) and how long (in minutes) this took to set up (only for participants receiving IV treatment)? How long (in minutes) did it take to administer the treatment, i.e. total infusion duration? How long (in minutes) was the patient in the Treatment Room for in total?" The value '999999' indicates 0 participants were analyzed.

End point type	Secondary

End point timeframe:
Day 1 of Cycles (Cyc) 1-6 (each cycle is 21 days)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	80		
Units: minutes				
median (full range (min-max))				
Cyc 1. Time for CVC Set Up (IV Only; n=4,0)	5.0 (4 to 6)	999999 (999999 to 999999)		
Cyc 1. Time for PICC Set Up (IV Only; n=1,0)	5.0 (5 to 5)	999999 (999999 to 999999)		
Cyc 1. Time for PVC Set Up (IV Only; n=50,0)	5.0 (1 to 40)	999999 (999999 to 999999)		
Cyc 1. Time Taken to Administer Treatment(n=79,79)	150.0 (60 to 396)	8.0 (2 to 17)		
Cyc 1. Time Patient Was in Treatment Room(n=79,79)	300.0 (90 to 450)	50.0 (8 to 240)		
Cyc 2. Time for CVC Set Up (IV Only; n=4,0)	5.0 (3 to 5)	999999 (999999 to 999999)		
Cyc 2. Time for PICC Set Up (IV Only; n=1,0)	3.0 (3 to 3)	999999 (999999 to 999999)		
Cyc 2. Time for PVC Set Up (IV Only; n=48,0)	5.0 (1 to 20)	999999 (999999 to 999999)		
Cyc 2. Time Taken to Administer Treatment(n=77,80)	90.0 (8 to 260)	8.0 (5 to 20)		
Cyc 2. Time Patient Was in Treatment Room(n=77,78)	153.0 (30 to 342)	40.0 (8 to 225)		
Cyc 3. Time for CVC Set Up (IV Only; n=5,0)	5.0 (3 to 10)	999999 (999999 to 999999)		
Cyc 3. Time for PICC Set Up (IV Only; n=1,0)	3.0 (3 to 3)	999999 (999999 to 999999)		
Cyc 3. Time for PVC Set Up (IV Only; n=48,0)	5.0 (1 to 30)	999999 (999999 to 999999)		
Cyc 3. Time Taken to Administer Treatment(n=79,80)	70.0 (30 to 240)	7.5 (4 to 16)		
Cyc 3. Time Patient Was in Treatment Room(n=79,79)	150.0 (105 to 330)	36.0 (5 to 327)		
Cyc 4. Time for CVC Set Up (IV Only; n=0,7)	999999 (999999 to 999999)	5.0 (2 to 10)		
Cyc 4. Time for PICC Set Up (IV Only; n=0,1)	999999 (999999 to 999999)	42.0 (42 to 42)		
Cyc 4. Time for PVC Set Up (IV Only; n=0,36)	999999 (999999 to 999999)	5.0 (1 to 20)		

Cyc 4. Time Taken to Administer Treatment(n=80,77)	8.0 (4 to 12)	60.0 (30 to 210)		
Cyc 4. Time Patient Was in Treatment Room(n=78,77)	45.0 (1 to 185)	150.0 (80 to 480)		
Cyc 5. Time for CVC Set Up (IV Only; n=0,5)	999999 (999999 to 999999)	3.0 (2 to 10)		
Cyc 5. Time for PICC Set Up (IV Only; n=0,1)	999999 (999999 to 999999)	10.0 (10 to 10)		
Cyc 5. Time for PVC Set Up (IV Only; n=0,38)	999999 (999999 to 999999)	5.0 (1 to 20)		
Cyc 5. Time Taken to Administer Treatment(n=79,77)	8.0 (3 to 14)	83.0 (30 to 200)		
Cyc 5. Time Patient Was in Treatment Room(n=79,77)	33.0 (8 to 135)	150.0 (95 to 343)		
Cyc 6. Time for CVC Set Up (IV Only; n=0,6)	999999 (999999 to 999999)	10.0 (1 to 91)		
Cyc 6. Time for PICC Set Up (IV Only; n=0,0)	999999 (999999 to 999999)	999999 (999999 to 999999)		
Cyc 6. Time for PVC Set Up (IV Only; n=0,43)	999999 (999999 to 999999)	5.0 (1 to 60)		
Cyc 6. Time Taken to Administer Treatment(n=79,80)	7.0 (3 to 11)	60.0 (5 to 275)		
Cyc 6. Time Patient Was in Treatment Room(n=79,80)	35.0 (10 to 150)	130.0 (45 to 330)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Healthcare Professionals (HCPs) by Their Responses on Perception of Impact of PH FDC SC on Clinical Management and Clinical Efficiency, Question 2 of the HCPQ - Treatment Room

End point title	Percentage of Healthcare Professionals (HCPs) by Their Responses on Perception of Impact of PH FDC SC on Clinical Management and Clinical Efficiency, Question 2 of the HCPQ - Treatment Room

End point description:

HCPs who administered study treatment responded at Cycle 6 of the Treatment Cross-Over Period to the following HCPQ-Treatment Room Question 2: "If all P+H IV infusions are switched to FDC SC injections, please indicate how strongly you agree or disagree with each of the following statements: a) Patients will be moved outside of infusion unit to receive FDC SC; b) FDC SC route will allow more flexible scheduling; c) More patients will be treated in the infusion unit; d) Waiting list for any P+H IV treatment at the infusion unit will be reduced; e) Staff resources will be redistributed to other departments of the hospital; f) There will still be sufficient interaction time between HCPs and patients; g) Staff will spend more time for further education/development; h) Staff will dedicate more time attending to administrative tasks for Perjeta-Herceptin patients; i) Patients will spend less time in the care unit; j) Administration by FDC SC injection is preferred by patients."

End point type	Secondary

End point timeframe:

Day 1 of Cycle 6 (each cycle is 21 days)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Healthcare Professionals	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79	80	159	
Units: Percentage of HCPs				
number (not applicable)				
Statement a): Strongly Disagree	11.4	21.3	16.4	
Statement a): Disagree	12.7	17.5	15.1	
Statement a): Neutral	8.9	3.8	6.3	
Statement a): Agree	26.6	16.3	21.4	
Statement a): Strongly Agree	22.8	22.5	22.6	
Statement a): Not Applicable	13.9	11.3	12.6	
Statement a): Answer Missing	3.8	7.5	5.7	
Statement b): Strongly Disagree	0.0	6.3	3.1	
Statement b): Disagree	7.6	10.0	8.8	
Statement b): Neutral	10.1	7.5	8.8	
Statement b): Agree	29.1	27.5	28.3	
Statement b): Strongly Agree	49.4	41.3	45.3	
Statement b): Not Applicable	0.0	0.0	0.0	
Statement b): Answer Missing	3.8	7.5	5.7	
Statement c): Strongly Disagree	1.3	3.8	2.5	
Statement c): Disagree	7.6	7.5	7.5	
Statement c): Neutral	17.7	12.5	15.1	
Statement c): Agree	29.1	31.3	30.2	
Statement c): Strongly Agree	36.7	37.5	37.1	
Statement c): Not Applicable	3.8	0.0	1.9	
Statement c): Answer Missing	3.8	7.5	5.7	
Statement d): Strongly Disagree	1.3	7.5	4.4	
Statement d): Disagree	8.9	7.5	8.2	
Statement d): Neutral	17.7	11.3	14.5	
Statement d): Agree	29.1	26.3	27.7	
Statement d): Strongly Agree	36.7	33.8	35.2	
Statement d): Not Applicable	2.5	5.0	3.8	
Statement d): Answer Missing	3.8	8.8	6.3	
Statement e): Strongly Disagree	15.2	10.0	12.6	
Statement e): Disagree	16.5	22.5	19.5	
Statement e): Neutral	17.7	22.5	20.1	
Statement e): Agree	19.0	11.3	15.1	
Statement e): Strongly Agree	20.3	18.8	19.5	
Statement e): Not Applicable	7.6	6.3	6.9	
Statement e): Answer Missing	3.8	8.8	6.3	
Statement f): Strongly Disagree	0.0	3.8	1.9	
Statement f): Disagree	6.3	3.8	5.0	
Statement f): Neutral	15.2	16.3	15.7	
Statement f): Agree	31.6	32.5	32.1	
Statement f): Strongly Agree	43.0	35.0	39.0	
Statement f): Not Applicable	0.0	0.0	0.0	

Statement f): Answer Missing	3.8	8.8	6.3	
Statement g): Strongly Disagree	0.0	5.0	2.5	
Statement g): Disagree	7.6	11.3	9.4	
Statement g): Neutral	31.6	23.8	27.7	
Statement g): Agree	20.3	22.5	21.4	
Statement g): Strongly Agree	35.4	27.5	31.4	
Statement g): Not Applicable	1.3	2.5	1.9	
Statement g): Answer Missing	3.8	7.5	5.7	
Statement h): Strongly Disagree	1.3	5.0	3.1	
Statement h): Disagree	11.4	16.3	13.8	
Statement h): Neutral	25.3	23.8	24.5	
Statement h): Agree	24.1	16.3	20.1	
Statement h): Strongly Agree	32.9	27.5	30.2	
Statement h): Not Applicable	1.3	3.8	2.5	
Statement h): Answer Missing	3.8	7.5	5.7	
Statement i): Strongly Disagree	0.0	0.0	0.0	
Statement i): Disagree	6.3	3.8	5.0	
Statement i): Neutral	1.3	5.0	3.1	
Statement i): Agree	27.8	22.5	25.2	
Statement i): Strongly Agree	60.8	60.0	60.4	
Statement i): Not Applicable	0.0	0.0	0.0	
Statement i): Answer Missing	3.8	8.8	6.3	
Statement j): Strongly Disagree	0.0	0.0	0.0	
Statement j): Disagree	8.9	1.3	5.0	
Statement j): Neutral	10.1	15.0	12.6	
Statement j): Agree	22.8	26.3	24.5	
Statement j): Strongly Agree	53.2	47.5	50.3	
Statement j): Not Applicable	1.3	1.3	1.3	
Statement j): Answer Missing	3.8	8.8	6.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Healthcare Professionals (HCPs) by Their Responses on Perception of Time/Resource Use and Convenience of Each Study Regimen, Questions 3 to 7 of the HCPQ - Treatment Room

End point title	Percentage of Healthcare Professionals (HCPs) by Their Responses on Perception of Time/Resource Use and Convenience of Each Study Regimen, Questions 3 to 7 of the HCPQ - Treatment Room

End point description:

Healthcare professionals (HCPs) who administered study treatment responded at Cycle 6 of the Treatment Cross-Over Period to the following HCPQ-Treatment Room Questions (Q) 3 to 7: "Looking back over the Perjeta-Herceptin treatment sessions, please indicate based on your opinion which administration method: Q3. Which Method Was Most Convenient for the Patient? Q4. Which Method Was Best for Optimizing Patient Care in Your Centre? Q5. Which Method Took the Least Time from Start to Finish of Administration? Q6. Which Method Required the Least Resource Use for Administration? Q7. Which Method Was Preferred by Patients?" The four available response options were: P+H IV, FDC SC, No Difference, and Unsure.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 6 (each cycle is 21 days)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Healthcare Professionals	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79	80	159	
Units: Percentage of HCPs				
number (not applicable)				
Q3. Answer: FDC SC	88.6	85.0	86.8	
Q3. Answer: P+H IV	6.3	1.3	3.8	
Q3. Answer: No Difference	2.5	5.0	3.8	
Q3. Answer: Unsure	0.0	7.5	3.8	
Q3. Answer: Missing	2.5	1.3	1.9	
Q4. Answer: FDC SC	79.7	78.8	79.2	
Q4. Answer: P+H IV	3.8	1.3	2.5	
Q4. Answer: No Difference	12.7	12.5	12.6	
Q4. Answer: Unsure	1.3	6.3	3.8	
Q4. Answer: Missing	2.5	1.3	1.9	
Q5. Answer: FDC SC	94.9	96.3	95.6	
Q5. Answer: P+H IV	0.0	0.0	0.0	
Q5. Answer: No Difference	2.5	2.5	2.5	
Q5. Answer: Unsure	0.0	0.0	0.0	
Q5. Answer: Missing	2.5	1.3	1.9	
Q6. Answer: FDC SC	83.5	88.8	86.2	
Q6. Answer: P+H IV	0.0	1.3	0.6	
Q6. Answer: No Difference	13.9	8.8	11.3	
Q6. Answer: Unsure	0.0	0.0	0.0	
Q6. Answer: Missing	2.5	1.3	1.9	
Q7. Answer: FDC SC	77.2	77.5	77.4	
Q7. Answer: P+H IV	7.6	5.0	6.3	
Q7. Answer: No Difference	2.5	2.5	2.5	
Q7. Answer: Unsure	10.1	13.8	11.9	
Q7. Answer: Missing	2.5	1.3	1.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Healthcare Professionals (HCPs) by Their Responses to Question 8 of the HCPQ - Treatment Room

End point title	Percentage of Healthcare Professionals (HCPs) by Their Responses to Question 8 of the HCPQ - Treatment Room

End point description:

Healthcare professionals (HCPs) who administered study treatment responded at Cycle 6 of the Treatment Cross-Over Period to the following HCPQ-Treatment Room Question 8: "How frequently would you offer or recommend FDC SC administration to your patients in the future?" The three available

response options were: Always, Sometimes, and Never.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 6 (each cycle is 21 days)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Healthcare Professionals	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79	80	159	
Units: Percentage of HCPs				
number (not applicable)				
Always	69.6	65.0	67.3	
Sometimes	26.6	33.8	30.2	
Never	1.3	0.0	0.6	
Missing	2.5	1.3	1.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Treatment Preparation According to Healthcare Professionals' Responses on Perception of Time by Treatment Cycle, Question 1 of the HCPQ - Drug Preparation Room

End point title	Duration of Treatment Preparation According to Healthcare Professionals' Responses on Perception of Time by Treatment Cycle, Question 1 of the HCPQ - Drug Preparation Room

End point description:

The Healthcare Professional Questionnaire (HCPQ)-Drug Preparation Room Question 1 was completed at each treatment cycle of the Treatment Cross-Over Period by the healthcare professionals (HCPs) within the pharmacy/drug preparation area where pertuzumab IV and trastuzumab IV and pertuzumab and trastuzumab FDC SC were prepared and dispensed for treating the study's participants. HCPs responded to the following question: "How long (in minutes) did it take to prepare the treatment for use?"

End point type	Secondary

End point timeframe:

Day 1 of Cycles 1-6 (each cycle is 21 days)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	80		
Units: minutes				
median (full range (min-max))				
Cycle 1 (n = 80, 79)	20.0 (3 to 60)	5.0 (1 to 50)		
Cycle 2 (n = 79, 80)	20.0 (3 to 60)	5.0 (1 to 30)		
Cycle 3 (n = 80, 79)	17.5 (3 to 90)	5.0 (1 to 40)		

Cycle 4 (n = 80, 80)	5.0 (1 to 30)	15.0 (3 to 49)		
Cycle 5 (n = 80, 79)	5.0 (1 to 35)	15.0 (3 to 50)		
Cycle 6 (n = 80, 78)	5.0 (1 to 40)	15.0 (3 to 50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Healthcare Professionals (HCPs) by Their Responses on Perception of Impact of PH FDC SC on Clinical Management and Clinical Efficiency, Question 2 of the HCPQ - Drug Preparation Room

End point title	Percentage of Healthcare Professionals (HCPs) by Their Responses on Perception of Impact of PH FDC SC on Clinical Management and Clinical Efficiency, Question 2 of the HCPQ - Drug Preparation Room

End point description:

Healthcare professionals (HCPs) who prepared study treatment within the pharmacy/drug preparation area responded at Cycle 6 of the Treatment Cross-Over Period to the following HCPQ-Drug Preparation Room Question 2: "If all P+H IV infusions are switched to FDC SC injections, please indicate how strongly you agree or disagree with each of the following statements: a) Staff will have increased availability for other tasks in the pharmacy; b) Administrative procedures around FDC SC will require less time; c) FDC SC formulations will provide more flexibility for staff in managing their workload; d) Due to ready-to-use FDC SC formulations, potential dosing errors will be avoided; e) Due to ready-to-use FDC SC formulations, there will be less drug wastage; f) Without having to reconstitute the drug, less storage space for FDC SC related supplies will be required in the pharmacy; g) Preparation procedures and associated time staff time commitment will be reduced."

End point type	Secondary

End point timeframe:

Day 1 of Cycle 6 (each cycle is 21 days)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Healthcare Professionals	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	80	160	
Units: Percentage of HCPs				
number (not applicable)				
Statement a): Strongly Disagree	1.3	1.3	1.3	
Statement a): Disagree	1.3	0.0	0.6	
Statement a): Neutral	8.8	6.3	7.5	
Statement a): Agree	28.8	28.8	28.8	
Statement a): Strongly Agree	52.5	48.8	50.6	
Statement a): Not Applicable	3.8	1.3	2.5	
Statement a): Answer Missing	3.8	13.8	8.8	
Statement b): Strongly Disagree	8.8	2.5	5.6	
Statement b): Disagree	3.8	3.8	3.8	
Statement b): Neutral	16.3	12.5	14.4	
Statement b): Agree	17.5	18.8	18.1	
Statement b): Strongly Agree	46.3	46.3	46.3	
Statement b): Not Applicable	2.5	2.5	2.5	
Statement b): Answer Missing	5.0	13.8	9.4	

Statement c): Strongly Disagree	0.0	1.3	0.6	
Statement c): Disagree	0.0	1.3	0.6	
Statement c): Neutral	15.0	11.3	13.1	
Statement c): Agree	28.8	23.8	26.3	
Statement c): Strongly Agree	50.0	47.5	48.8	
Statement c): Not Applicable	1.3	1.3	1.3	
Statement c): Answer Missing	5.0	6.3	9.4	
Statement d): Strongly Disagree	1.3	1.3	1.3	
Statement d): Disagree	1.3	6.3	3.8	
Statement d): Neutral	5.0	6.3	5.6	
Statement d): Agree	26.3	20.0	23.1	
Statement d): Strongly Agree	60.0	52.5	56.3	
Statement d): Not Applicable	1.3	1.3	1.3	
Statement d): Answer Missing	5.0	12.5	8.8	
Statement e): Strongly Disagree	1.3	1.3	1.3	
Statement e): Disagree	1.3	2.5	1.9	
Statement e): Neutral	11.3	6.3	8.8	
Statement e): Agree	21.3	22.5	21.9	
Statement e): Strongly Agree	58.8	51.3	55.0	
Statement e): Not Applicable	1.3	2.5	1.9	
Statement e): Answer Missing	5.0	13.8	9.4	
Statement f): Strongly Disagree	0.0	1.3	0.6	
Statement f): Disagree	3.8	5.0	4.4	
Statement f): Neutral	16.3	7.5	11.9	
Statement f): Agree	20.0	28.8	24.4	
Statement f): Strongly Agree	53.8	42.5	48.1	
Statement f): Not Applicable	1.3	1.3	1.3	
Statement f): Answer Missing	5.0	13.8	9.4	
Statement g): Strongly Disagree	0.0	1.3	0.6	
Statement g): Disagree	0.0	0.0	0.0	
Statement g): Neutral	8.8	5.0	6.9	
Statement g): Agree	30.0	32.5	31.3	
Statement g): Strongly Agree	52.5	45.0	48.8	
Statement g): Not Applicable	3.8	2.5	3.1	
Statement g): Answer Missing	5.0	13.8	9.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Healthcare Professionals (HCPs) by Their Responses on Perception of Time/Resource Use of Each Study Regimen, Questions 3 and 4 of the HCPQ - Drug Preparation Room

End point title	Percentage of Healthcare Professionals (HCPs) by Their Responses on Perception of Time/Resource Use of Each Study Regimen, Questions 3 and 4 of the HCPQ - Drug Preparation Room

End point description:

Healthcare professionals (HCPs) who prepared study treatment within the pharmacy/drug preparation area responded at Cycle 6 of the Treatment Cross-Over Period to the following HCPQ-Drug Preparation Room Questions 3 and 4: "Looking back over the Perjeta-Herceptin treatment sessions, please indicate

based on your opinion which administration method: Q3. Was quickest from start to end of preparation to finish of administration (excluding observation period)?; Q4. Required less resource use for preparation and administration, for example nursing time, facility costs, equipment etc?" The three available response options were: P+H IV, FDC SC, and No Difference.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 6 (each cycle is 21 days)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Healthcare Professionals	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	80	160	
Units: Percentage of HCPs				
number (not applicable)				
Q3. Answer: FDC SC	92.5	82.5	87.5	
Q3. Answer: P+H IV	0.0	1.3	0.6	
Q3. Answer: No Difference	1.3	1.3	1.3	
Q3. Answer: Missing	6.3	15.0	10.6	
Q4. Answer: FDC SC	93.8	80.0	86.9	
Q4. Answer: P+H IV	0.0	0.0	0.0	
Q4. Answer: No Difference	0.0	5.0	2.5	
Q4. Answer: Missing	6.3	15.0	10.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Health-Related Quality of Life (HRQoL) as Assessed by the Global Health Status (GHS)/HRQoL Scale Score of the the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30)

End point title	Change From Baseline Over Time in Health-Related Quality of Life (HRQoL) as Assessed by the Global Health Status (GHS)/HRQoL Scale Score of the the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30)

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[2]	80[3]	159[4]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	71.62 (± 17.98)	76.77 (± 15.22)	74.21 (± 16.79)	
Change from BL at Cycle 3 Day 1 (n=77,80,157)	0.54 (± 16.63)	0.00 (± 14.88)	0.27 (± 15.72)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	1.10 (± 20.25)	-1.16 (± 16.44)	-0.05 (± 18.38)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	2.82 (± 16.30)	1.76 (± 17.87)	2.29 (± 17.05)	
Change from BL at 1.5 Years (n=72,74,146)	7.18 (± 21.73)	6.42 (± 16.92)	6.79 (± 19.38)	
Change from BL at 2 Years (n=73,73,146)	6.16 (± 19.45)	4.11 (± 17.46)	5.14 (± 18.45)	
Change from BL at 3 Years (n=68,65,133)	7.23 (± 16.85)	6.54 (± 20.12)	6.89 (± 18.45)	

Notes:

[2] - n = participants with non-missing data at baseline and a given timepoint.

[3] - n = participants with non-missing data at baseline and a given timepoint.

[4] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Physical Functioning Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Physical Functioning Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[5]	80[6]	159[7]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	84.22 (± 14.91)	88.08 (± 13.86)	86.16 (± 14.48)	
Change from BL at Cycle 3 Day 1 (n=79,80,159)	1.77 (± 12.97)	-0.42 (± 11.09)	0.67 (± 12.08)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	1.93 (± 16.61)	0.51 (± 12.11)	1.20 (± 14.46)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	3.85 (± 13.65)	1.22 (± 17.69)	2.54 (± 15.79)	
Change from BL at 1.5 Years (n=72,74,146)	5.44 (± 17.29)	4.05 (± 14.08)	4.74 (± 15.71)	
Change from BL at 2 Years (n=73,73,146)	4.38 (± 18.57)	3.56 (± 13.84)	3.97 (± 16.32)	
Change from BL at 3 Years (n=68,65,133)	3.33 (± 13.99)	1.64 (± 15.41)	2.51 (± 14.67)	

Notes:

[5] - n = participants with non-missing data at baseline and a given timepoint.

[6] - n = participants with non-missing data at baseline and a given timepoint.

[7] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Role Functioning Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Role Functioning Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[8]	80[9]	159[10]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	79.54 (± 25.45)	77.08 (± 26.17)	78.30 (± 25.76)	
Change from BL at Cycle 3 Day 1 (n=79,80,159)	3.80 (± 24.01)	9.58 (± 26.49)	6.71 (± 25.37)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	6.36 (± 24.03)	8.44 (± 28.10)	7.42 (± 26.12)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	6.81 (± 24.00)	12.44 (± 34.24)	9.62 (± 29.60)	
Change from BL at 1.5 Years (n=72,74,146)	9.49 (± 29.31)	16.89 (± 30.41)	13.24 (± 30.00)	
Change from BL at 2 Years (n=73,73,146)	11.64 (± 29.22)	10.96 (± 31.08)	11.30 (± 30.07)	
Change from BL at 3 Years (n=68,65,133)	8.09 (± 26.78)	12.82 (± 31.43)	10.40 (± 29.13)	

Notes:

[8] - n = participants with non-missing data at baseline and a given timepoint.

[9] - n = participants with non-missing data at baseline and a given timepoint.

[10] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Emotional Functioning Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Emotional Functioning Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[11]	80[12]	159[13]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	82.07 (± 16.99)	82.08 (± 18.52)	82.08 (± 17.72)	
Change from BL at Cycle 3 Day 1 (n=78,80,158)	-1.28 (± 15.26)	1.35 (± 16.53)	0.05 (± 15.92)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	0.99 (± 20.04)	-0.32 (± 17.42)	0.32 (± 18.70)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	-1.17 (± 15.77)	2.46 (± 22.77)	0.65 (± 19.60)	
Change from BL at 1.5 Years (n=72,74,146)	0.93 (± 23.05)	3.94 (± 21.95)	2.45 (± 22.47)	
Change from BL at 2 Years (n=73,73,146)	2.74 (± 21.61)	0.99 (± 25.89)	1.86 (± 23.78)	
Change from BL at 3 Years (n=68,65,133)	3.55 (± 21.08)	1.15 (± 26.43)	2.38 (± 23.78)	

Notes:

[11] - n = participants with non-missing data at baseline and a given timepoint.

[12] - n = participants with non-missing data at baseline and a given timepoint.

[13] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Cognitive Functioning Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Cognitive Functioning Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[14]	80[15]	159[16]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	85.86 (± 17.92)	84.58 (± 18.90)	85.22 (± 18.37)	
Change from BL at Cycle 3 Day 1 (n=78,80,158)	-0.64 (± 17.08)	-1.25 (± 21.18)	-0.95 (± 19.21)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	-3.29 (± 18.86)	-1.69 (± 21.94)	-2.47 (± 20.44)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	-7.75 (± 21.79)	-1.64 (± 23.09)	-4.69 (± 22.58)	
Change from BL at 1.5 Years (n=72,74,146)	-3.47 (± 20.16)	-0.45 (± 22.41)	-1.94 (± 21.31)	
Change from BL at 2 Years (n=73,73,146)	-2.51 (± 20.54)	0.46 (± 21.69)	-1.03 (± 21.10)	
Change from BL at 3 Years (n=68,65,133)	-2.45 (± 20.42)	-3.59 (± 26.76)	-3.01 (± 23.64)	

Notes:

[14] - n = participants with non-missing data at baseline and a given timepoint.

[15] - n = participants with non-missing data at baseline and a given timepoint.

[16] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Social Functioning Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Social Functioning Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	78[17]	80[18]	158[19]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=78,80,158)	77.99 (± 22.39)	80.00 (± 21.28)	79.01 (± 21.79)	
Change from BL at Cycle 3 Day 1 (n=77,80,157)	5.41 (± 24.40)	7.08 (± 20.84)	6.26 (± 22.60)	
Change from BL at Cycle 6 Day 1 (n=75,79,154)	6.44 (± 25.39)	2.53 (± 20.16)	4.44 (± 22.87)	
Change from BL at Cycle 15/Last Cycle(n=70,71,141)	9.05 (± 23.86)	6.57 (± 23.98)	7.80 (± 23.87)	
Change from BL at 1.5 Years (n=71,74,145)	12.21 (± 29.41)	12.61 (± 18.05)	12.41 (± 24.20)	
Change from BL at 2 Years (n=72,73,145)	15.28 (± 25.29)	12.10 (± 23.12)	13.68 (± 24.19)	
Change from BL at 3 Years (n=67,65,132)	11.94 (± 25.76)	13.33 (± 23.24)	12.63 (± 24.46)	

Notes:

[17] - n = participants with non-missing data at baseline and a given timepoint.

[18] - n = participants with non-missing data at baseline and a given timepoint.

[19] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Fatigue Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Fatigue Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[20]	80[21]	159[22]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	24.47 (± 19.28)	19.58 (± 18.31)	22.01 (± 18.90)	
Change from BL at Cycle 3 Day 1 (n=79,80,159)	-0.14 (± 17.66)	2.71 (± 14.92)	1.29 (± 16.35)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	-3.22 (± 17.85)	4.08 (± 19.91)	0.50 (± 19.22)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	-3.44 (± 18.36)	-0.78 (± 24.22)	-2.11 (± 21.46)	
Change from BL at 1.5 Years (n=72,74,146)	-9.26 (± 20.43)	-6.31 (± 18.76)	-7.76 (± 19.59)	
Change from BL at 2 Years (n=73,73,146)	-6.54 (± 25.51)	-3.96 (± 23.52)	-5.25 (± 24.49)	
Change from BL at 3 Years (n=68,65,133)	-7.68 (± 21.66)	-3.08 (± 23.45)	-5.43 (± 22.58)	

Notes:

[20] - n = participants with non-missing data at baseline and a given timepoint.

[21] - n = participants with non-missing data at baseline and a given timepoint.

[22] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Nausea and Vomiting Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Nausea and Vomiting Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[23]	80[24]	159[25]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	2.11 (± 7.24)	3.33 (± 9.71)	2.73 (± 8.57)	
Change from BL at Cycle 3 Day 1 (n=79,80,159)	0.21 (± 9.80)	1.46 (± 11.62)	0.84 (± 10.74)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	1.54 (± 11.92)	0.00 (± 11.32)	0.75 (± 11.61)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	1.88 (± 12.13)	0.47 (± 10.53)	1.17 (± 11.34)	
Change from BL at 1.5 Years (n=72,74,146)	0.46 (± 11.18)	-0.90 (± 11.67)	-0.23 (± 11.41)	
Change from BL at 2 Years (n=73,73,146)	-0.23 (± 11.28)	-1.14 (± 10.88)	-0.68 (± 11.05)	
Change from BL at 3 Years (n=68,65,133)	-1.23 (± 9.69)	-0.26 (± 11.97)	-0.75 (± 10.83)	

Notes:

[23] - n = participants with non-missing data at baseline and a given timepoint.

[24] - n = participants with non-missing data at baseline and a given timepoint.

[25] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Pain Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Pain Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[26]	80[27]	159[28]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	17.72 (± 24.94)	14.38 (± 19.26)	16.04 (± 22.26)	
Change from BL at Cycle 3 Day 1 (n=79,80,159)	0.00 (± 27.86)	0.42 (± 22.02)	0.21 (± 25.02)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	-2.41 (± 25.92)	3.16 (± 20.34)	0.43 (± 23.34)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	-2.82 (± 25.04)	0.47 (± 26.72)	-1.17 (± 25.85)	
Change from BL at 1.5 Years (n=72,74,146)	-1.62 (± 33.47)	-0.90 (± 23.71)	-1.26 (± 28.84)	
Change from BL at 2 Years (n=73,73,146)	-1.83 (± 30.25)	-4.34 (± 23.25)	-3.08 (± 26.91)	
Change from BL at 3 Years (n=68,65,133)	-1.72 (± 26.88)	-2.56 (± 29.79)	-2.13 (± 28.23)	

Notes:

[26] - n = participants with non-missing data at baseline and a given timepoint.

[27] - n = participants with non-missing data at baseline and a given timepoint.

[28] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Dyspnoea Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Dyspnoea Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[29]	80[30]	159[31]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	6.75 (± 15.45)	5.00 (± 15.09)	5.87 (± 15.25)	
Change from BL at Cycle 3 Day 1 (n=79,80,159)	-0.42 (± 14.61)	1.67 (± 11.74)	0.63 (± 13.24)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	1.32 (± 15.81)	4.64 (± 15.77)	3.01 (± 15.83)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	1.41 (± 19.05)	2.35 (± 16.26)	1.88 (± 17.65)	
Change from BL at 1.5 Years (n=72,74,146)	-0.46 (± 10.46)	1.80 (± 16.45)	0.68 (± 13.82)	
Change from BL at 2 Years (n=73,73,146)	1.83 (± 16.56)	1.83 (± 10.96)	1.83 (± 14.00)	
Change from BL at 3 Years (n=68,65,133)	1.47 (± 13.42)	1.54 (± 14.94)	1.50 (± 14.13)	

Notes:

[29] - n = participants with non-missing data at baseline and a given timepoint.

[30] - n = participants with non-missing data at baseline and a given timepoint.

[31] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Insomnia Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Insomnia Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[32]	80[33]	159[34]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	21.94 (± 24.97)	22.50 (± 25.86)	22.22 (± 25.34)	
Change from BL at Cycle 3 Day 1 (n=79,80,159)	2.95 (± 26.25)	-0.42 (± 27.81)	1.26 (± 27.01)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	5.26 (± 29.34)	-1.69 (± 30.15)	1.72 (± 29.86)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	3.76 (± 32.15)	-5.63 (± 30.85)	-0.94 (± 31.75)	
Change from BL at 1.5 Years (n=72,74,146)	1.85 (± 30.07)	-2.25 (± 31.85)	-0.23 (± 30.95)	
Change from BL at 2 Years (n=73,73,146)	6.85 (± 35.56)	-0.91 (± 31.90)	2.97 (± 33.89)	
Change from BL at 3 Years (n=68,65,133)	1.47 (± 33.79)	-1.54 (± 34.58)	0.00 (± 34.08)	

Notes:

[32] - n = participants with non-missing data at baseline and a given timepoint.

[33] - n = participants with non-missing data at baseline and a given timepoint.

[34] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Appetite Loss Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Appetite Loss Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[35]	80[36]	159[37]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	8.44 (± 14.59)	11.67 (± 23.18)	10.06 (± 19.40)	
Change from BL at Cycle 3 Day 1 (n=79,80,159)	3.38 (± 23.02)	-2.92 (± 19.26)	0.21 (± 21.38)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	0.00 (± 18.86)	-1.69 (± 17.62)	-0.86 (± 18.20)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	-4.69 (± 17.18)	-6.10 (± 23.44)	-5.40 (± 20.49)	
Change from BL at 1.5 Years (n=72,74,146)	-4.63 (± 20.41)	-7.66 (± 19.54)	-6.16 (± 19.96)	
Change from BL at 2 Years (n=73,73,146)	-5.48 (± 15.73)	-3.20 (± 20.91)	-4.34 (± 18.47)	
Change from BL at 3 Years (n=68,65,133)	-5.39 (± 15.89)	-6.67 (± 22.97)	-6.02 (± 19.61)	

Notes:

[35] - n = participants with non-missing data at baseline and a given timepoint.

[36] - n = participants with non-missing data at baseline and a given timepoint.

[37] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Constipation Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Constipation Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[38]	80[39]	159[40]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	8.44 (± 16.42)	9.58 (± 21.99)	9.01 (± 19.37)	
Change from BL at Cycle 3 Day 1 (n=79,80,159)	0.00 (± 15.10)	-3.33 (± 18.06)	-1.68 (± 16.69)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	0.88 (± 20.35)	-2.53 (± 18.31)	-0.86 (± 19.35)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	0.00 (± 20.31)	-1.41 (± 22.14)	-0.70 (± 21.18)	
Change from BL at 1.5 Years (n=72,74,146)	0.00 (± 17.69)	0.45 (± 28.93)	0.23 (± 23.97)	
Change from BL at 2 Years (n=73,73,146)	5.94 (± 26.26)	-2.74 (± 27.08)	1.60 (± 26.93)	
Change from BL at 3 Years (n=68,65,133)	0.49 (± 20.36)	2.56 (± 26.55)	1.50 (± 23.52)	

Notes:

[38] - n = participants with non-missing data at baseline and a given timepoint.

[39] - n = participants with non-missing data at baseline and a given timepoint.

[40] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Diarrhoea Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Diarrhoea Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[41]	80[42]	159[43]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	12.24 (± 22.76)	8.75 (± 20.36)	10.48 (± 21.59)	
Change from BL at Cycle 3 Day 1 (n=78,80,158)	4.70 (± 25.04)	9.58 (± 29.14)	7.17 (± 27.22)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	4.39 (± 23.31)	5.49 (± 25.28)	4.95 (± 24.26)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	2.82 (± 25.66)	2.35 (± 26.62)	2.58 (± 26.06)	
Change from BL at 1.5 Years (n=72,74,146)	-8.33 (± 23.57)	-4.50 (± 20.88)	-6.39 (± 22.25)	
Change from BL at 2 Years (n=73,73,146)	-8.22 (± 26.52)	-5.48 (± 20.80)	-6.85 (± 23.79)	
Change from BL at 3 Years (n=68,65,133)	-9.80 (± 25.79)	-5.13 (± 21.43)	-7.52 (± 23.79)	

Notes:

[41] - n = participants with non-missing data at baseline and a given timepoint.

[42] - n = participants with non-missing data at baseline and a given timepoint.

[43] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in the Financial Difficulties Scale Score of the EORTC QLQ-C30

End point title	Change From Baseline Over Time in the Financial Difficulties Scale Score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 questionnaire consisted of 30 questions covering treatment-related symptoms, functioning, and GHS/HRQoL. Questions were answered by participants on a scale from 1 to 4 or 1 to 7. Raw scores were transformed to scale scores that ranged from 0 to 100 where a higher scale score indicating a higher response (i.e., on the functioning and GHS/QoL scales a higher score meant better functioning/QoL, whereas on the symptom scales a higher score meant greater [worse] symptoms). The EORTC QLQ-C30 data was scored according to the EORTC scoring manual (Fayers 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score was to be computed consistent with the scoring manuals and published validation reports. For subscales with less than 50% of the items completed, the subscale was to be considered as missing.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Cycle 1); Day 1 of Cycles 3, 6, and 15 (or last treatment cycle; each cycle is 21 days); 1.5, 2, and 3 years (up to 3 years)

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	79[44]	80[45]	159[46]	
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (BL): Value at Visit (n=79,80,159)	23.63 (± 27.30)	22.08 (± 28.04)	22.85 (± 27.59)	
Change from BL at Cycle 3 Day 1 (n=78,80,158)	-2.99 (± 20.23)	-2.92 (± 24.42)	-2.95 (± 22.38)	
Change from BL at Cycle 6 Day 1 (n=76,79,155)	-4.39 (± 20.61)	0.00 (± 24.46)	-2.15 (± 22.69)	
Change from BL at Cycle 15/Last Cycle(n=71,71,142)	-8.45 (± 25.02)	-8.45 (± 25.65)	-8.45 (± 25.24)	
Change from BL at 1.5 Years (n=72,74,146)	-13.89 (± 30.00)	-11.26 (± 26.62)	-12.56 (± 28.27)	
Change from BL at 2 Years (n=73,73,146)	-15.98 (± 27.84)	-12.79 (± 28.13)	-14.38 (± 27.93)	
Change from BL at 3 Years (n=68,65,133)	-14.71 (± 32.26)	-8.21 (± 29.48)	-11.53 (± 30.99)	

Notes:

[44] - n = participants with non-missing data at baseline and a given timepoint.

[45] - n = participants with non-missing data at baseline and a given timepoint.

[46] - n = participants with non-missing data at baseline and a given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Summary for Assessment of Switching Between the FDC SC and IV Formulations: Number of Participants with at Least One Adverse Event During the Treatment Cross-Over Period by Treatment Arm and Treatment Received

End point title	Safety Summary for Assessment of Switching Between the FDC SC and IV Formulations: Number of Participants with at Least One Adverse Event During the Treatment Cross-Over Period by Treatment Arm and Treatment Received

End point description:

Investigators used the NCI CTCAE v4.0 grading scale for assessing adverse event (AE) severity; if not listed, AE severity was graded as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe or medically significant; Grade 4 = life-threatening; Grade 5 = death related to AE. Severity and seriousness are not synonymous and investigators independently assessed these criteria for each AE. Investigators also determined whether an AE was considered to be related to the study drug. Adverse events to monitor were defined based on known risks associated with the study drugs and included: hypersensitivity reactions, administration-related reactions (ARRs), cardiac dysfunction, diarrhea grade ≥3, rash/skin reactions, mucositis, interstitial lung disease (ILD), (febrile) neutropenia, pulmonary events that may occur as a result of an ARR, and pregnancy/neonatal related. Multiple occurrences of AEs were counted only once per participant. LVEF = left ventricular ejection fraction

End point type	Secondary

End point timeframe:

From Day 1 of Cycle 1 to the end of Cycle 3 of Cross-Over Period; from Day 1 of Cycle 4 to the end of Cycle 6 of Cross-Over Period (1 cycle is 21 days)

End point values	Arm A: Treatment With P+H IV (Cycles 1–3)	Arm A: Treatment With PH FDC SC (Cycles 4–6)	Arm B: Treatment With PH FDC SC (Cycles 1–3)	Arm B: Treatment With P+H IV (Cycles 4–6)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	80	80	80
Units: Participants				
Any Adverse Event (AE)	62	60	62	51
AE with Fatal Outcome	0	0	0	0
Related AE with Fatal Outcome	0	0	0	0
Grade 3 to 5 AE	1	1	3	4
Related Grade 3 to 5 AE	1	0	1	0
Cardiac AE (Including LVEF Events)	1	2	3	2
Serious AE	1	1	1	5
Anaphylaxis and Hypersensitivity AE, All Grades	0	2	1	0
Anaphylaxis and Hypersensitivity AE, Grade ≥3	0	0	0	0
Administration Related Reaction (ARR), All Grades	7	14	24	2
Administration Related Reaction (ARR), Grade ≥3	0	0	0	0
Cardiac Dysfunction AE, All Grades	2	1	3	3
Cardiac Dysfunction AE, Grade ≥3	1	0	0	0
Diarrhea Grade ≥3	0	0	1	0
Rash/Skin Reactions	0	0	0	0
Mucositis	0	0	0	0
Pulmonary Events (ARR), All Grades	18	8	4	8
Pulmonary Events (ARR), Grade ≥3	0	0	1	0
Pregnancy and Neonatal Related AEs, All Grades	0	0	1	0
Pregnancy and Neonatal Related AEs, Grade ≥3	0	0	0	0
Interstitial Lung Disease (ILD)	0	0	0	0
Neutropenia/Febrile Neutropenia, All Grades	4	1	2	3
Neutropenia/Febrile Neutropenia, Grade ≥3	0	0	0	0
Local Infusion Site Reaction	1	0	0	0
Systemic Infusion Site Reaction	5	0	0	1
Local Injection Site Reaction	0	12	24	0
Systemic Injection Site Reaction	0	2	1	0
AE Leading to Any Study Treatment Discontinuation	0	1	0	0
AE Leading to PH FDC SC Discontinuation	0	1	0	0
AE Leading to Pertuzumab IV Discontinuation	0	0	0	0
AE Leading to Trastuzumab IV Discontinuation	0	0	0	0
AE Leading to Any Study Trx Interrupt./Dose Reduc.	1	0	2	3

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Summary of the FDC SC and IV Formulations: Number of Participants with at Least One Adverse Event During the Treatment Cross-Over and Treatment Continuation Periods

End point title	Safety Summary of the FDC SC and IV Formulations: Number of Participants with at Least One Adverse Event During the Treatment Cross-Over and Treatment Continuation Periods

End point description:

Investigators used the NCI CTCAE v4.0 grading scale for assessing adverse event (AE) severity; if not listed, AE severity was graded as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe or medically significant; Grade 4 = life-threatening; Grade 5 = death related to AE. Severity and seriousness are not synonymous and investigators independently assessed these criteria for each AE. Investigators also determined whether an AE was considered to be related to the study drug. Adverse events to monitor were defined based on known risks associated with the study drugs and included: hypersensitivity reactions, administration-related reactions (ARRs), cardiac dysfunction, diarrhea grade ≥3, rash/skin reactions, mucositis, interstitial lung disease (ILD), (febrile) neutropenia, pulmonary events that may occur as a result of an ARR, and pregnancy/neonatal related. Multiple occurrences of AEs were counted only once per participant. LVEF = left ventricular ejection fraction

End point type	Secondary

End point timeframe:

From Day 1 of Cycle 1 to end of Cycle 6 of the Treatment Cross-Over Period; from Day 1 of Cycle 7 up to the completion of 18 cycles of neo/adjuvant anti-HER2 treatment in the Treatment Continuation Period (1 cycle is 21 days)

End point values	P+H IV: Treatment Cross-Over Period	PH FDC SC: Treatment Cross-Over Period	P+H IV: Treatment Continuation Period	PH FDC SC: Treatment Continuation Period
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	160	160	21	138
Units: Participants				
Any Adverse Event (AE)	113	122	14	92
AE with Fatal Outcome	0	0	0	0
Related AE with Fatal Outcome	0	0	0	0
Grade 3 to 5 AE	5	4	2	7
Related Grade 3 to 5 AE	1	1	0	0
Cardiac AE (Including LVEF Events)	3	5	1	1
Serious AE	6	2	0	4
Anaphylaxis and Hypersensitivity AE, All Grades	0	3	0	2
Anaphylaxis and Hypersensitivity AE, Grade ≥3	0	0	0	0
Administration Related Reaction (ARR), All Grades	9	38	1	16
Administration Related Reaction (ARR), Grade ≥3	0	0	0	0
Cardiac Dysfunction AE, All Grades	5	4	1	2
Cardiac Dysfunction AE, Grade ≥3	1	0	0	0
Diarrhea Grade ≥3	0	1	0	0
Rash/Skin Reactions	0	0	0	0
Mucositis	0	0	0	0
Pulmonary Events (ARR), All Grades	26	12	5	13
Pulmonary Events (ARR), Grade ≥3	0	1	0	0

Pregnancy and Neonatal Related AEs, All Grades	0	1	0	0
Pregnancy and Neonatal Related AEs, Grade ≥3	0	0	0	0
Interstitial Lung Disease (ILD), All Grades	0	0	0	1
Interstitial Lung Disease (ILD), Grade ≥3	0	0	0	0
Neutropenia/Febrile Neutropenia, All Grades	7	3	1	5
Neutropenia/Febrile Neutropenia, Grade ≥3	0	0	0	1
Local Infusion Site Reaction	1	0	0	0
Systemic Infusion Site Reaction	6	0	1	0
Local Injection Site Reaction	0	36	0	13
Systemic Injection Site Reaction	0	3	0	2
AE Leading to Any Study Treatment Discontinuation	0	1	1	0
AE Leading to PH FDC SC Discontinuation	0	1	0	0
AE Leading to Pertuzumab IV Discontinuation	0	0	1	0
AE Leading to Trastuzumab IV Discontinuation	0	0	1	0
AE Leading to Any Study Trx Interrupt./Dose Reduc.	4	2	1	8

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with at Least One Event of Heart Failure with the FDC SC and IV Formulations During the Treatment Cross-Over and Treatment Continuation Periods

End point title	Number of Participants with at Least One Event of Heart Failure with the FDC SC and IV Formulations During the Treatment Cross-Over and Treatment Continuation Periods

End point description:

Heart failure is defined as a disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do only at an elevation in the filling pressure. Any adverse event of symptomatic left ventricular systolic dysfunction (LVSD; also referred to as heart failure) occurring during the study was to be reported as a serious adverse event.

End point type	Secondary

End point timeframe:

From Day 1 of Cycle 1 to end of Cycle 6 of the Treatment Cross-Over Period; from Day 1 of Cycle 7 up to the completion of 18 cycles of neo/adjuvant anti-HER2 treatment in the Treatment Continuation Period (1 cycle is 21 days)

End point values	P+H IV: Treatment Cross-Over Period	PH FDC SC: Treatment Cross-Over Period	P+H IV: Treatment Continuation Period	PH FDC SC: Treatment Continuation Period
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	160	160	21	138
Units: Participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with at Least One Event of Ejection Fraction Decreased with the FDC SC and IV Formulations During the Treatment Cross-Over and Treatment Continuation Periods

End point title	Number of Participants with at Least One Event of Ejection Fraction Decreased with the FDC SC and IV Formulations During the Treatment Cross-Over and Treatment Continuation Periods

End point description:

Left ventricular ejection fraction (LVEF) is the measurement of how much blood is being pumped out of the left ventricle of the heart (the main pumping chamber) with each contraction. All participants who enrolled in this study must have had a baseline LVEF ≥55%. Verbatim description of adverse events was mapped to Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. The MedDRA preferred term of 'ejection fraction decreased' is defined as an LVEF decrease of at least 10 percentage points from baseline and to below 50%.

End point type	Secondary

End point timeframe:

Baseline; Day 1 of Cycles 4, 7, and 11 (each cycle is 21 days); End of Treatment and Follow-Up visits (up to 3 years)

End point values	P+H IV: Treatment Cross-Over Period	PH FDC SC: Treatment Cross-Over Period	P+H IV: Treatment Continuation Period	PH FDC SC: Treatment Continuation Period
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	160	160	21	138
Units: Participants	3	4	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Targeted Vital Signs Outside the Normal Limits Among Those Without an Abnormality at Baseline During the Treatment Cross-Over and Treatment Continuation Periods

End point title	Number of Participants with Targeted Vital Signs Outside the Normal Limits Among Those Without an Abnormality at Baseline During the Treatment Cross-Over and Treatment Continuation Periods

End point description:

The number of participants at any post-baseline timepoint with abnormal readings outside the normal range for vital signs of diastolic and systolic blood pressure (BP), pulse rate, respiratory rate, and body temperature were summarized according the specified direction of the abnormal reading (high or low). In this analysis, participants are grouped by study arm and treatment received during the Cross-Over Period, and only by treatment received during the Continuation Period. The number analyzed (denominator) in the results table represents participants without the specified abnormal vital sign at baseline.

End point type	Secondary

End point timeframe:

Pre-dose at Day 1 of Cycles 1 (baseline), 4, and 7, and end of treatment (up to 18 cycles; 1 cycle is 21 days)

End point values	Arm A: Treatment With P+H IV (Cycles 1–3)	Arm A: Treatment With PH FDC SC (Cycles 4–6)	Arm B: Treatment With PH FDC SC (Cycles 1–3)	Arm B: Treatment With P+H IV (Cycles 4–6)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	80	80	80
Units: Participants				
Diastolic BP - Low (n=80,77,80,80,20,137)	0	0	0	0
Diastolic BP - High (n=80,77,78,78,20,135)	2	2	0	0
Systolic BP - Low (n=80,77,80,80,20,137)	0	0	0	0
Systolic BP - High (n=77,74,75,75,20,129)	8	7	3	3
Pulse Rate - Low (n=80,77,80,80,20,137)	0	0	0	0
Pulse Rate - High (n=75,72,75,75,19,128)	1	0	0	1
Respiratory Rate - Low (n=80,77,80,79,20,137)	0	0	0	0
Respiratory Rate - High (n=80,77,79,78,20,136)	1	0	2	2
Temperature - Low (n=54,51,39,39,12,80)	22	17	10	13
Temperature - High (n=80,77,80,80,21,137)	0	0	1	0

End point values	P+H IV: Treatment Continuation Period	PH FDC SC: Treatment Continuation Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	138		
Units: Participants				
Diastolic BP - Low (n=80,77,80,80,20,137)	0	0		
Diastolic BP - High (n=80,77,78,78,20,135)	0	3		
Systolic BP - Low (n=80,77,80,80,20,137)	0	0		

Systolic BP - High (n=77,74,75,75,20,129)	1	12		
Pulse Rate - Low (n=80,77,80,80,20,137)	0	0		
Pulse Rate - High (n=75,72,75,75,19,128)	1	1		
Respiratory Rate - Low (n=80,77,80,79,20,137)	0	0		
Respiratory Rate - High (n=80,77,79,78,20,136)	0	4		
Temperature - Low (n=54,51,39,39,12,80)	4	34		
Temperature - High (n=80,77,80,80,21,137)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Chemistry and Hematology Laboratory Test Result Shifts from NCI-CTCAE Grade 0–2 at Baseline to Grade 3–4 Post-Baseline During the Treatment Cross-Over and Treatment Continuation Periods

End point title	Number of Participants with Chemistry and Hematology Laboratory Test Result Shifts from NCI-CTCAE Grade 0–2 at Baseline to Grade 3–4 Post-Baseline During the Treatment Cross-Over and Treatment Continuation Periods

End point description:

Laboratory data for targeted chemistry and hematology parameters were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0); Grade 0 is normal and Grades 1 to 4 represent worsening levels of the laboratory parameter outside of the normal range in the specified direction of the abnormality (e.g., high is an increase, low is a decrease). The results table presents the shifts in the number of participants with NCI-CTCAE Grade 0–2 at baseline to Grade 3–4 post-baseline for the targeted parameters according to the specified direction of the abnormality outside of the normal range (high or low). Participants with missing baseline values were counted as Grade 0–2 at baseline. SGOT/AST = aspartate aminotransferase; SGPT/ALT = alanine aminotransferase

End point type	Secondary

End point timeframe:

Pre-dose at Day 1 of Cycles 1 (baseline), 4, 7, 11, 15, and end of treatment (up to 18 cycles; 1 cycle is 21 days)

End point values	Arm A: Treatment With P+H IV (Cycles 1–3)	Arm A: Treatment With PH FDC SC (Cycles 4–6)	Arm B: Treatment With PH FDC SC (Cycles 1–3)	Arm B: Treatment With P+H IV (Cycles 4–6)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	80	80	80	80
Units: Participants				
Alkaline Phosphatase - High (n=78,79,78,78,21,136)	0	0	0	0
SGPT/ALT - High (n=78,79,78,79,21,136)	0	0	0	0
SGOT/AST - High (n=77,78,79,79,21,136)	0	0	0	0

Creatinine - High (n=80,78,79,77,21,136)	0	0	0	0
Bilirubin, Total - High (n=76,79,79,79,21,136)	0	0	0	0
Hemoglobin - Low (n=80,78,79,80,21,136)	0	0	0	0
Hemoglobin - High (n=80,78,79,80,21,136)	0	0	0	0
Neutrophils, Total,Abs - Low(n=80,78,79,80,21,136)	0	0	0	0
Platelet - Low (n=80,78,79,80,21,136)	0	0	0	0
Total Leukocyte Count - Low (n=80,78,79,80,21,136)	0	0	0	0
Total Leukocyte Count - High(n=80,78,79,80,21,136)	0	0	0	0

End point values	P+H IV: Treatment Continuation Period	PH FDC SC: Treatment Continuation Period		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	138		
Units: Participants				
Alkaline Phosphatase - High (n=78,79,78,78,21,136)	0	0		
SGPT/ALT - High (n=78,79,78,79,21,136)	0	0		
SGOT/AST - High (n=77,78,79,79,21,136)	0	0		
Creatinine - High (n=80,78,79,77,21,136)	0	0		
Bilirubin, Total - High (n=76,79,79,79,21,136)	0	0		
Hemoglobin - Low (n=80,78,79,80,21,136)	0	0		
Hemoglobin - High (n=80,78,79,80,21,136)	0	0		
Neutrophils, Total,Abs - Low(n=80,78,79,80,21,136)	0	2		
Platelet - Low (n=80,78,79,80,21,136)	0	0		
Total Leukocyte Count - Low (n=80,78,79,80,21,136)	0	1		
Total Leukocyte Count - High(n=80,78,79,80,21,136)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Were Event-Free for Overall Survival, Overall and by Treatment Sequence

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were Event-Free for Overall Survival, Overall and by Treatment Sequence

End point description:

Overall survival is defined as the time from randomization to death due to any cause. Participants who were not reported as having died at the time of analysis were censored at the date when they were last known to be alive. Participants who did not have post-baseline information were censored at the date of randomization +1 day. Kaplan-Meier methodology was used to estimate the percentage of participants who were alive (event-free) at 12, 24, and 36 months.

End point type	Secondary

End point timeframe:

At 12, 24, and 36 months

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80[47]	80[48]	160[49]	
Units: Percentage of participants				
number (confidence interval 95%)				
12 Months (n= 79, 78, 157)	100.00 (100.00 to 100.00)	100.00 (100.00 to 100.00)	100.00 (100.00 to 100.00)	
24 Months (n= 76, 75, 151)	98.73 (96.27 to 100.00)	100.00 (100.00 to 100.00)	99.36 (98.12 to 100.00)	
36 Months (n= 44, 53, 97)	97.44 (93.93 to 100.00)	100.00 (100.00 to 100.00)	98.71 (96.92 to 100.00)	

Notes:

[47] - n = number remaining at risk for an event

[48] - n = number remaining at risk for an event

[49] - n = number remaining at risk for an event

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Event for Overall Survival, Overall and by Treatment Sequence

End point title	Number of Participants with an Event for Overall Survival, Overall and by Treatment Sequence

End point description:

Overall survival (OS) is defined as the time from randomization to death due to any cause. The number of participants who had an OS event (i.e., died) while on study is reported.

End point type	Secondary

End point timeframe:

Up to 3 years, 10 months

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	80	160	
Units: Participants	2	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Were Event-Free for Invasive Disease-Free Survival Including Second Primary Non-Breast Cancer, Overall and by Treatment Sequence

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were Event-Free for Invasive Disease-Free Survival Including Second Primary Non-Breast Cancer, Overall and by Treatment Sequence

End point description:

Invasive Disease-Free Survival is defined as the time from randomization to the first occurrence of one of the following events: ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, and death from any cause. Second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) was included as an event. Participants who had not experienced invasive disease at the time of analysis were censored: i) at the time of the last clinical breast examination if they had post-baseline clinical breast examination; ii) on the date of randomization +1 day if no post-baseline clinical breast examination. Kaplan-Meier methodology was used to estimate the percentage of participants who were event-free at 12, 24, and 36 months.

End point type	Secondary

End point timeframe:

At 12, 24, and 36 months

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80[50]	80[51]	160[52]	
Units: Percentage of participants				
number (confidence interval 95%)				
12 Months (n= 75, 78, 153)	94.94 (90.10 to 99.77)	100.00 (100.00 to 100.00)	97.46 (95.00 to 99.92)	
24 Months (n= 71, 72, 143)	92.37 (86.50 to 98.24)	97.38 (93.80 to 100.00)	94.87 (91.40 to 98.33)	
36 Months (n= 36, 46, 82)	91.05 (84.72 to 97.38)	96.03 (91.63 to 100.00)	93.53 (89.65 to 97.41)	

Notes:

[50] - n = number remaining at risk for an event

[51] - n = number remaining at risk for an event

[52] - n = number remaining at risk for an event

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Event for Invasive Disease-Free Survival Including Second Primary Non-Breast Cancer, Overall and by Treatment Sequence

End point title	Number of Participants with an Event for Invasive Disease-Free Survival Including Second Primary Non-Breast Cancer, Overall and by Treatment Sequence

End point description:

Invasive Disease-Free Survival is defined as the time from randomization to the first occurrence of one of the following events: ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, and death from any cause. Second primary non-breast invasive cancer (with the exception of non-melanoma skin cancers and in situ carcinoma of any site) was included as an event.

End point type	Secondary

End point timeframe:

Up to 3 years, 10 months

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	80	160	
Units: Participants	7	5	12	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Event for Invasive Disease-Free Survival, Overall and by Treatment Sequence

End point title	Number of Participants with an Event for Invasive Disease-Free Survival, Overall and by Treatment Sequence

End point description:

Invasive Disease-Free Survival is defined as the time from randomization to the first occurrence of one of the following events: ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, and death from any cause. Ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in situ carcinomas and non-melanoma skin cancers) were not counted as recurrence.

End point type	Secondary

End point timeframe:

Up to 3 years, 10 months

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	80	160	
Units: Participants	6	5	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Were Event-Free for Invasive Disease-Free Survival, Overall and by Treatment Sequence

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were Event-Free for Invasive Disease-Free Survival, Overall and by Treatment Sequence

End point description:

Invasive Disease-Free Survival is defined as the time from randomization to the first occurrence of one of the following events: ipsilateral invasive breast tumour recurrence, ipsilateral local-regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, and death from any cause. Ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in situ carcinomas and non-melanoma skin cancers) were not counted as recurrence. Participants who had not experienced invasive disease at the time of analysis were censored: i) at the time of the last clinical breast examination if they had post-baseline clinical breast examination; ii) on the date of randomization +1 day if no post-baseline clinical breast examination. Kaplan-Meier methodology was used to estimate the percentage of participants who were event-free at 12, 24, and 36 months.

End point type	Secondary

End point timeframe:

At 12, 24, and 36 months

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80[53]	80[54]	160[55]	
Units: Percentage of participants				
number (confidence interval 95%)				
12 Months (n= 76, 78, 154)	96.20 (91.99 to 100.00)	100.00 (100.00 to 100.00)	98.10 (95.96 to 100.00)	
24 Months (n= 72, 72, 144)	93.64 (88.24 to 99.03)	97.38 (93.80 to 100.00)	95.51 (92.25 to 98.76)	
36 Months (n= 36, 46, 82)	92.32 (86.41 to 98.23)	96.03 (91.63 to 100.00)	94.17 (90.47 to 97.87)	

Notes:

[53] - n = number remaining at risk for an event

[54] - n = number remaining at risk for an event

[55] - n = number remaining at risk for an event

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Were Event-Free for Distant Disease-Free Survival, Overall and by Treatment Sequence

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Were Event-Free for Distant Disease-Free Survival, Overall and by Treatment Sequence

End point description:

Distant disease-free survival (DDFS) is defined as the time from randomization to the date of distant breast cancer recurrence (i.e., evidence of breast cancer in any anatomic site other than for ipsilateral [loco-regional] invasive breast cancer recurrence that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer). Participants who had not experienced invasive disease at the time of analysis were censored: i) at the time of the last clinical breast examination if they had post-baseline clinical breast examination; ii) on the date of randomization +1 day if no post-baseline clinical breast examination. Kaplan-Meier methodology was used to estimate the percentage of participants who were event-free at 12, 24, and 36 months.

End point type	Secondary

End point timeframe:

Up to 3 years

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80[56]	80[57]	160[58]	
Units: Percentage of participants				
number (confidence interval 95%)				
12 Months (n= 77, 78, 155)	97.47 (94.00 to 100.00)	100.00 (100.00 to 100.00)	98.73 (96.98 to 100.00)	
24 Months (n= 73, 72, 145)	94.90 (90.04 to 99.77)	97.38 (93.80 to 100.00)	96.14 (93.11 to 99.17)	
36 Months (n= 37, 46, 83)	93.58 (88.14 to 99.03)	96.03 (91.63 to 100.00)	94.80 (91.30 to 98.31)	

Notes:

[56] - n = number remaining at risk for an event

[57] - n = number remaining at risk for an event

[58] - n = number remaining at risk for an event

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with an Event for Distant Disease-Free Survival, Overall and by Treatment Sequence

End point title	Number of Participants with an Event for Distant Disease-Free Survival, Overall and by Treatment Sequence

End point description:

Distant disease-free survival (DDFS) is defined as the time from randomization to the date of distant breast cancer recurrence (i.e., evidence of breast cancer in any anatomic site other than for ipsilateral [loco-regional] invasive breast cancer recurrence that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer).

End point type	Secondary

End point timeframe:

Up to 3 years, 10 months

End point values	A: P+H IV Followed by PH FDC SC	B: PH FDC SC Followed by P+H IV	All Participants	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	80	80	160	
Units: Participants	5	4	9	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Cross-Over:3+3 cycles P+H IV & PH FDC SC; Continuation: rest of 18 total cycles P+H IV or PH FDC SC; All Participants: from first dose through 28 days after last dose. Follow-up: from 29 days after last dose to 7 months (AEs), or end of follow-up (deaths)

Adverse event reporting additional description:

After initiation of study treatment, all AEs were to be reported until 28 days after the last dose. In the Follow-Up Period, the following AEs were to be reported: study drug-related serious AEs; AEs of special interest, heart failure, pregnancies, non−breast-related second primary malignancies and deaths, irrespective of causal relationship.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Pertuzumab IV and Trastuzumab IV: Cross-Over Period

Reporting group description:

This safety analysis population includes all participants from arms A and B who received up to 3 cycles (1 cycle = 21 days) of treatment with pertuzumab IV and trastuzumab IV during the Treatment Cross-Over Period of the study.

Reporting group title	Pertuzumab and Trastuzumab FDC SC: Cross-Over Period

Reporting group description:

This safety analysis population includes all participants from arms A and B who received up to 3 cycles (1 cycle = 21 days) of treatment with the pertuzumab and trastuzumab fixed dose combination administered subcutaneously (FDC SC) during the Treatment Cross-Over Period of the study.

Reporting group title	Pertuzumab IV and Trastuzumab IV: Continuation Period

Reporting group description:

This safety analysis population includes all participants from arms A and B who, following completion of the Treatment Cross-Over Period, chose to receive pertuzumab IV and trastuzumab IV during the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment).

Reporting group title	Pertuzumab and Trastuzumab FDC SC: Continuation Period

Reporting group description:

This safety analysis population includes all participants from arms A and B who, following completion of the Treatment Cross-Over Period, chose to receive the pertuzumab and trastuzumab fixed dose combination administered subcutaneously (FDC SC) during the Treatment Continuation Period for the remaining anti-HER2 treatment cycles (18 planned cycles in total, including pre-study neoadjuvant treatment).

Reporting group title	All Participants: All Study Treatment Periods

Reporting group description:

This safety analysis population includes all participants from Arms A and B who received at least one dose of treatment with pertuzumab IV and trastuzumab IV (P+H IV) and/or the pertuzumab and trastuzumab fixed-dose combination for subcutaneous administration (PH FDC SC) across any of the treatment periods during the study through 28 days after the last dose of study treatment.

Reporting group title	Follow-Up Period

Reporting group description:

This safety analysis population includes all participants from Arms A and B who had received at least one dose of any study treatment and had not discontinued from the study prior to entering the follow-up period. The timeframe of the follow-up period started at 29 days after the last dose of study treatment until the end of follow-up (≥3 years after randomization of the last participant).

Serious adverse events	Pertuzumab IV and Trastuzumab IV: Cross-Over Period	Pertuzumab and Trastuzumab FDC SC: Cross-Over Period	Pertuzumab IV and Trastuzumab IV: Continuation Period
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 160 (3.75%)	2 / 160 (1.25%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 160 (0.63%)	1 / 160 (0.63%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 160 (0.00%)	0 / 160 (0.00%)	0 / 21 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 160 (0.00%)	1 / 160 (0.63%)	0 / 21 (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
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 160 (0.63%)	0 / 160 (0.00%)	0 / 21 (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
Erysipelas			
subjects affected / exposed	1 / 160 (0.63%)	0 / 160 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cellulitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 160 (0.00%)	0 / 21 (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
Bronchopulmonary aspergillosis			

subjects affected / exposed	0 / 160 (0.00%)	0 / 160 (0.00%)	0 / 21 (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	1 / 160 (0.63%)	0 / 160 (0.00%)	0 / 21 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 160 (0.63%)	0 / 160 (0.00%)	0 / 21 (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
COVID-19			
subjects affected / exposed	0 / 160 (0.00%)	0 / 160 (0.00%)	0 / 21 (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

Serious adverse events	Pertuzumab and Trastuzumab FDC SC: Continuation Period	All Participants: All Study Treatment Periods	Follow-Up Period
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 138 (2.90%)	11 / 160 (6.88%)	1 / 159 (0.63%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events			
Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 138 (0.00%)	2 / 160 (1.25%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 138 (0.00%)	0 / 160 (0.00%)	1 / 159 (0.63%)
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			
Asthma			

subjects affected / exposed	0 / 138 (0.00%)	1 / 160 (0.63%)	0 / 159 (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
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 138 (0.72%)	2 / 160 (1.25%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	2 / 138 (1.45%)	2 / 160 (1.25%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cellulitis			
subjects affected / exposed	0 / 138 (0.00%)	1 / 160 (0.63%)	0 / 159 (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
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 138 (0.72%)	1 / 160 (0.63%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 138 (0.00%)	1 / 160 (0.63%)	0 / 159 (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 respiratory tract infection			
subjects affected / exposed	0 / 138 (0.00%)	1 / 160 (0.63%)	0 / 159 (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
COVID-19			
subjects affected / exposed	1 / 138 (0.72%)	1 / 160 (0.63%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Pertuzumab IV and Trastuzumab IV: Cross-Over Period	Pertuzumab and Trastuzumab FDC SC: Cross-Over Period	Pertuzumab IV and Trastuzumab IV: Continuation Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 160 (38.75%)	84 / 160 (52.50%)	10 / 21 (47.62%)
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	27 / 160 (16.88%)	17 / 160 (10.63%)	0 / 21 (0.00%)
occurrences (all)	29	17	0
Vascular disorders			
Hot flush			
subjects affected / exposed	6 / 160 (3.75%)	9 / 160 (5.63%)	0 / 21 (0.00%)
occurrences (all)	6	10	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 160 (1.88%)	5 / 160 (3.13%)	2 / 21 (9.52%)
occurrences (all)	3	6	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 160 (5.00%)	9 / 160 (5.63%)	1 / 21 (4.76%)
occurrences (all)	8	10	3
Injection site reaction			
subjects affected / exposed	0 / 160 (0.00%)	36 / 160 (22.50%)	0 / 21 (0.00%)
occurrences (all)	0	50	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 160 (10.63%)	15 / 160 (9.38%)	4 / 21 (19.05%)
occurrences (all)	20	19	4
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 160 (1.25%)	3 / 160 (1.88%)	3 / 21 (14.29%)
occurrences (all)	3	3	3
Pruritus			
subjects affected / exposed	7 / 160 (4.38%)	3 / 160 (1.88%)	0 / 21 (0.00%)
occurrences (all)	8	3	0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 160 (3.75%)	8 / 160 (5.00%)	3 / 21 (14.29%)
occurrences (all)	8	9	3
Bone pain			
subjects affected / exposed	0 / 160 (0.00%)	0 / 160 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Myalgia			
subjects affected / exposed	6 / 160 (3.75%)	3 / 160 (1.88%)	2 / 21 (9.52%)
occurrences (all)	6	3	2
Pain in extremity			
subjects affected / exposed	1 / 160 (0.63%)	4 / 160 (2.50%)	2 / 21 (9.52%)
occurrences (all)	1	5	2

Non-serious adverse events	Pertuzumab and Trastuzumab FDC SC: Continuation Period	All Participants: All Study Treatment Periods	Follow-Up Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 138 (34.06%)	125 / 160 (78.13%)	2 / 159 (1.26%)
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	1 / 138 (0.72%)	44 / 160 (27.50%)	0 / 159 (0.00%)
occurrences (all)	1	47	0
Vascular disorders			
Hot flush			
subjects affected / exposed	3 / 138 (2.17%)	16 / 160 (10.00%)	0 / 159 (0.00%)
occurrences (all)	3	19	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 138 (0.72%)	10 / 160 (6.25%)	0 / 159 (0.00%)
occurrences (all)	1	13	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 138 (5.07%)	19 / 160 (11.88%)	0 / 159 (0.00%)
occurrences (all)	8	29	0
Injection site reaction			

subjects affected / exposed	13 / 138 (9.42%)	44 / 160 (27.50%)	0 / 159 (0.00%)
occurrences (all)	28	78	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 138 (10.87%)	37 / 160 (23.13%)	0 / 159 (0.00%)
occurrences (all)	23	66	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 138 (1.45%)	10 / 160 (6.25%)	0 / 159 (0.00%)
occurrences (all)	3	12	0
Pruritus			
subjects affected / exposed	7 / 138 (5.07%)	14 / 160 (8.75%)	0 / 159 (0.00%)
occurrences (all)	7	18	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 138 (4.35%)	23 / 160 (14.38%)	1 / 159 (0.63%)
occurrences (all)	6	26	1
Bone pain			
subjects affected / exposed	0 / 138 (0.00%)	2 / 160 (1.25%)	0 / 159 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	1 / 138 (0.72%)	12 / 160 (7.50%)	1 / 159 (0.63%)
occurrences (all)	1	12	1
Pain in extremity			
subjects affected / exposed	4 / 138 (2.90%)	9 / 160 (5.63%)	1 / 159 (0.63%)
occurrences (all)	5	13	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported