ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 06/30/2016

ClinicalTrials.gov ID: NCT01401166

Study Identification

Unique Protocol ID:	MO22982
Brief Title:	Patients' Preference of Herceptin (Trastuzumab) Subcutaneous Versus Intravenous Administration in HER2-positive Early Breast Cancer
Official Title:	A Randomized, Multi-centre Cross-over Study to Evaluate Patient Preference and Health Care Professional (HCP) Satisfaction With Subcutaneous (SC) Administration of Trastuzumab in HER2-positive Early Breast Cancer (EBC)
Secondary IDs:	

Study Status

Record Verification:	June 2016
Overall Status:	Completed
Study Start:	October 2011
Primary Completion:	May 2013 [Actual]
Study Completion:	December 2015 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes

Applicable Trial?:	Section 801 Clinical Trial? No Delayed Posting?
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: to be added Board Name: COMITATO ETICO DELL`IRCCS FONDAZIONE S. RAFFAELE DEL MONTE TABOR DI MILANO Board Affiliation: IRCCS FONDAZIONE S. RAFFAELE DEL MONTE TABOR DI MILANO Phone: 00 39 02 26432911 Email: alfredo.anzani@hsr.it
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Italy: Ministry of Health

Study Description

Brief Summary:	This randomized, open-label, crossover study evaluated participants' preference and healthcare professional satisfaction with trastuzumab (Herceptin) subcutaneous (sc) versus intravenous (iv) administration in participants with HER2-positive early breast cancer.
Detailed Description:	Participants were randomized to receive either trastuzumab 600 mg SC or trastuzumab 6 mg/kg IV every 3 weeks for Cycles 1-4, then crossover to the other treatment administration for Cycles 5-8. For the remaining up to 10 cycles, participants in Cohort 1 were administered trastuzumab 6 mg/kg IV every 3 weeks and participants in Cohort 2 were administered trastuzumab 600 mg SC every 3 weeks. Participants in Cohort 1, who had at least 2 treatment cycles remaining of their 18-cycle treatment course after the crossover period, were offered the opportunity to self-administer trastuzumab 600 mg subcutaneously using the single-injection device on Day 1 of each 3-week cycle under the direction of a trained health care practitioner.

Conditions

Conditions:	Breast Cancer
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Crossover Assignment

Number of Arms:	2
Masking:	Open Label
Allocation:	Non-Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	488 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Trastuzumab subcutaneously then trastuzumab intravenously Participants received trastuzumab on Day 1 of each 3-week cycle for 18 cycles. During cycles 1-4 of the crossover period, they received trastuzumab 600 mg subcutaneously (SC) and during cycles 5-8, they received trastuzumab 6 mg/kg intravenously (IV). In the other 10 cycles, participants received either trastuzumab 6 mg/kg IV (Cohort 1) or trastuzumab 600 mg SC vial (Cohort 2).	Drug: Trastuzumab subcutaneously Trastuzumab subcutaneously was supplied in either a single-use injection device or in vials for injection with a hand-held syringe. Other Names: • Herceptin Drug: Trastuzumab intravenously Trastuzumab intravenously was provided in vials as a freeze-dried lyophilisate. Other Names: • Herceptin Biological/Vaccine: Recombinant humanized hyaluronidase Both the single-use injection device and the vials for injection with a hand-held syringe contained 2000 units/mL of recombinant humanized hyaluronidase as a permeation enhancer.
Experimental: Trastuzumab intravenously then trastuzumab subcutaneously Participants received trastuzumab on Day 1 of each 3-week cycle for 18 cycles. During cycles 1-4 of the crossover period, they received trastuzumab 6 mg/kg intravenously (IV) and during cycles 5-8, they received trastuzumab 600 mg subcutaneously (SC). In case Cycle 1 of the crossover period was the first cycle of trastuzumab treatment, a loading dose of trastuzumab 8 mg/kg IV was administered. In the other 10 cycles, participants received either trastuzumab 6 mg/kg IV (Cohort 1) or trastuzumab 600 mg SC vial (Cohort 2).	Drug: Trastuzumab subcutaneously Trastuzumab subcutaneously was supplied in either a single-use injection device or in vials for injection with a hand-held syringe. Other Names: • Herceptin Drug: Trastuzumab intravenously Trastuzumab intravenously was provided in vials as a freeze-dried lyophilisate. Other Names: • Herceptin Biological/Vaccine: Recombinant humanized hyaluronidase Both the single-use injection device and the vials for injection with a hand-held syringe contained 2000 units/mL of recombinant humanized hyaluronidase as a permeation enhancer.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Female

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Female patients, ≥ 18 years of age.
- HER2-positive breast cancer.
- No evidence of residual, locally recurrent, or metastatic disease after completion of surgery and chemotherapy (neoadjuvant or adjuvant).
- All adjuvant chemotherapy must be completed; adjuvant radiotherapy may be ongoing.
- Patients who have already received intravenous Herceptin must have at least 8 out of the total planned 18 3-week cycles remaining.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

Exclusion Criteria:

- History of other malignancy, except for ductal carcinoma in situ of the breast, curatively treated carcinoma in situ of the cervix or basal cell carcinoma, or other curatively treated malignancies that have been disease-free for at least 5 years.
- Inadequate bone marrow function.
- Impaired liver function.
- Inadequate renal function.
- Serious cardiovascular disease.
- Human immunodeficiency virus (HIV) or hepatitis B (HBV) or C (HCV) infection.
- Prior maximum cumulative dose of doxorubicin > 360 mg/m^2 or epirubicin > 720 mg/m^2 or equivalent.

Contacts/Locations

Study Officials: Clinical Trials
Study Director
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Locations: Russian Federation
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References

Citations:

Links:

Study Data/Documents:

Participant Flow

Recruitment Details	248 participants were randomized into the study in Cohort 1 (of which 244 were treated) and 240 participants were randomized into the study in Cohort 2 (of which 239 were treated).
Pre-Assignment Details	4 participants in the trastuzumab subcutaneously then trastuzumab intravenously group and 1 participant in the trastuzumab intravenously then trastuzumab subcutaneously group did not receive any treatment and were not included in Participant Flow.

Reporting Groups

	Description
Trastuzumab Subcutaneously Then Trastuzumab Intravenously	Participants received trastuzumab on Day 1 of each 3-week cycle for 8 cycles of the crossover period. During cycles 1-4, they received trastuzumab 600 mg subcutaneously (SC) and during cycles 5-8, they received trastuzumab 6 mg/kg intravenously (IV).
Trastuzumab Intravenously Then Trastuzumab Subcutaneously	Participants received trastuzumab on Day 1 of each 3-week cycle for 8 cycles of the crossover period. During cycles 1-4, they received trastuzumab 6 mg/kg intravenously (IV) and during cycles 5-8, they received trastuzumab 600 mg subcutaneously (SC). In case Cycle 1 of the cross-over period was the first cycle of trastuzumab treatment, a loading dose of trastuzumab 8 mg/kg IV was administered.
Cohort 1	Participants received trastuzumab 6 mg/kg intravenously on Day 1 of each 3-week cycle for up to 10 remaining cycles. Participants in Cohort 1, who had at least 2 treatment cycles remaining of their 18-cycle treatment course, were offered the opportunity to self-administer trastuzumab 600 mg subcutaneously using the single-injection device on Day 1 of each 3-week cycle under the direction of a trained health care practitioner. Following the end of treatment, participants were followed for 3 years for safety.
Cohort 2	Participants received trastuzumab 600 mg/kg subcutaneously on Day 1 of each 3-week cycle for up to 10 remaining cycles. Following the end of treatment, participants were followed for 3 years for safety.

Crossover Treatment 1

	Trastuzumab Subcutaneously Then Trastuzumab Intravenously	Trastuzumab Intravenously Then Trastuzumab Subcutaneously	Cohort 1	Cohort 2
Started	243	240	0 [1]	0 [1]
Completed	243	240	0	0
Not Completed	0	0	0	0

[1] There were no participants in this reporting group in this period.

Crossover Treatment 2

	Trastuzumab Subcutaneously Then Trastuzumab Intravenously	Trastuzumab Intravenously Then Trastuzumab Subcutaneously	Cohort 1	Cohort 2
Started	241 [1]	237 [1]	0 [2]	0 [2]
Completed	241	237	0	0
Not Completed	0	0	0	0

[1] Not all participants who completed crossover treatment 1 started crossover treatment 2.
[2] There were no participants in this reporting group in this period.

Continuation Period

	Trastuzumab Subcutaneously Then Trastuzumab Intravenously	Trastuzumab Intravenously Then Trastuzumab Subcutaneously	Cohort 1	Cohort 2
Started	0 [1]	0 [1]	226 [2]	206 [2]
Completed	0	0	226	119
Not Completed	0	0	0	87

[1] There were no participants in this reporting group in this period.
[2] Not all participants who completed crossover treatment 2 started the continuation period.

Safety Follow-up Period

	Trastuzumab Subcutaneously Then Trastuzumab Intravenously	Trastuzumab Intravenously Then Trastuzumab Subcutaneously	Cohort 1	Cohort 2
Started	0 [1]	0 [1]	248 [2]	153 [3]
Completed	0	0	22	12
Not Completed	0	0	226	141

[1] There were no participants in this reporting group in this period.
[2] All 248 randomized participants in Cohort 1 started the safety follow-up period.
[3] Some of the participants in Cohort 2 were still receiving treatment and did not start this period.

Baseline Characteristics

Analysis Population Description

Safety population: All participants who received at least 1 dose of trastuzumab.

Reporting Groups

	Description
Trastuzumab Subcutaneously and Intravenously	Participants received trastuzumab on Day 1 of each 3-week cycle for 18 cycles. They either received trastuzumab 600 mg subcutaneously (SC) for 4 cycles followed by trastuzumab 6 mg/kg intravenously (IV) for 4 cycles or trastuzumab 6 mg/kg intravenously (IV) for 4 cycles followed by trastuzumab 600 mg subcutaneously (SC) for 4 cycles. For up to 10 remaining cycles, participants received either trastuzumab 6 mg/kg IV or trastuzumab 600 mg SC using the single-use injection device (Cohort 1) or trastuzumab 600 mg SC (Cohort 2).

Baseline Measures

	Trastuzumab Subcutaneously and Intravenously
Number of Participants	483
Age, Continuous [units: years] Mean (Standard Deviation)	53.1 (11.13)
Gender, Male/Female [units: participants]	
Female	483
Male	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Participants' Preferred Method of Drug Administration
Measure Description	The preferred method of drug administration, intravenous or subcutaneous, was assessed in trial-specific telephone interviews with each study participant conducted after the end of the crossover period. Specifically, the participant was asked “All things considered, which method of administration did you prefer?” Reported is the percentage of participants who preferred each method of drug administration.
Time Frame	Week 24
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All participants who received trastuzumab both intravenously and subcutaneously and who completed the trial-specific telephone interview conducted after the end of the crossover period.

Reporting Groups

	Description
Trastuzumab Subcutaneously and Intravenously	Participants received trastuzumab on Day 1 of each 3-week cycle for 8 cycles. They either received trastuzumab 600 mg subcutaneously (SC) for 4 cycles followed by trastuzumab 6 mg/kg intravenously (IV) for 4 cycles or trastuzumab 6 mg/kg intravenously (IV) for 4 cycles followed by trastuzumab 600 mg subcutaneously (SC) for 4 cycles. In case Cycle 1 of the crossover period was the first cycle of trastuzumab treatment, a loading dose of trastuzumab 8 mg/kg IV was administered.

Measured Values

	Trastuzumab Subcutaneously and Intravenously
Number of Participants Analyzed	467
Participants' Preferred Method of Drug Administration [units: Percentage of participants]	
Subcutaneous	88.9
Intravenous	9.6
No preference	1.5

2. Secondary Outcome Measure:

Measure Title	Healthcare Practitioners' Most Satisfied Method of Drug Administration
Measure Description	The method of drug administration with which healthcare practitioners were most satisfied, intravenous or subcutaneous, was assessed at the end of the crossover period by the response to the question in the healthcare practitioner questionnaire “All things considered, with which method of administration were you most satisfied?”. Reported is the percentage of healthcare practitioners who were most satisfied with each method of drug administration.
Time Frame	Week 24
Safety Issue?	No

Analysis Population Description

Healthcare practitioner population: All healthcare practitioners who participated in the study and completed the healthcare practitioner questionnaire.

Reporting Groups

	Description
Trastuzumab Subcutaneously and Intravenously	Participants received trastuzumab on Day 1 of each 3-week cycle for 8 cycles. They either received trastuzumab 600 mg subcutaneously (SC) for 4 cycles followed by trastuzumab 6 mg/kg intravenously (IV) for 4 cycles or trastuzumab 6 mg/kg intravenously (IV) for 4 cycles followed by trastuzumab 600 mg subcutaneously (SC) for 4 cycles. In case Cycle 1 of the crossover period was the first cycle of trastuzumab treatment, a loading dose of trastuzumab 8 mg/kg IV was administered.

Measured Values

	Trastuzumab Subcutaneously and Intravenously
Number of Participants Analyzed	235
Healthcare Practitioners' Most Satisfied Method of Drug Administration [units: Percentage of healthcare practitioners]	
Subcutaneous	77.0
Intravenous	23.0

3. Secondary Outcome Measure:

Measure Title	Healthcare Practitioners' Perceived Time to Perform Each Method of Drug Administration
Measure Description	Healthcare professionals were asked to rate the amount of time it took to administer trastuzumab subcutaneously and intravenously in the following time block categories: < 5, 6-10, 11-15, 16-20, > 20 minutes, Not sure, and Unknown. Reported is the percentage of healthcare practitioners who rated the amount of time in each of the categories.
Time Frame	Week 24
Safety Issue?	No

Analysis Population Description

Healthcare practitioner population: All healthcare practitioners who participated in the study and completed the healthcare practitioner questionnaire.

Reporting Groups

	Description
Trastuzumab Subcutaneously and Intravenously	Participants received trastuzumab on Day 1 of each 3-week cycle for 8 cycles. They either received trastuzumab 600 mg subcutaneously (SC) for 4 cycles followed by trastuzumab 6 mg/kg intravenously (IV) for 4 cycles or trastuzumab 6 mg/kg intravenously (IV) for 4 cycles followed by trastuzumab 600 mg subcutaneously (SC) for 4 cycles. In case Cycle 1 of the crossover period was the first cycle of trastuzumab treatment, a loading dose of trastuzumab 8 mg/kg IV was administered.

Measured Values

	Trastuzumab Subcutaneously and Intravenously
Number of Participants Analyzed	235
Healthcare Practitioners' Perceived Time to Perform Each Method of Drug Administration [units: Percentage of healthcare practitioners]	
Subcutaneously < 5 minutes	44.3
Subcutaneously 6-10 minutes	46.4
Subcutaneously 11-15 minutes	3.4
Subcutaneously 16-20 minutes	0.4
Subcutaneously > 20 minutes	0.4
Subcutaneously not sure	0.0
Subcutaneously unknown	5.1
Intravenously < 5 minutes	11.1
Intravenously 6-10 minutes	9.8
Intravenously 11-15 minutes	3.8
Intravenously 16-20 minutes	44.3
Intravenously > 20 minutes	22.1
Intravenously not sure	5.1
Intravenously unknown	3.8

4. Secondary Outcome Measure:

Measure Title	Event-free Survival
Measure Description	Event-free survival is defined as the time from randomization to a local, regional, or distant recurrence of the original breast cancer, occurrence of contralateral breast cancer, or death due to any cause. As event-free survival is a long-term Outcome Measure and participants have received trastuzumab both intravenously and subcutaneously, the results are presented for all participants as a single group.
Time Frame	Baseline to the end of the study (up to 3 years, 2 weeks)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All participants who received trastuzumab both intravenously and subcutaneously and who completed the trial-specific telephone interview conducted after the end of the crossover period.

Reporting Groups

	Description
Trastuzumab Subcutaneously and Intravenously	Participants received trastuzumab on Day 1 of each 3-week cycle for 18 cycles. They either received trastuzumab 600 mg subcutaneously (SC) for 4 cycles followed by trastuzumab 6 mg/kg intravenously (IV) for 4 cycles or trastuzumab 6 mg/kg intravenously (IV) for 4 cycles followed by trastuzumab 600 mg subcutaneously (SC) for 4 cycles. For up to 10 remaining cycles, participants received either trastuzumab 6 mg/kg IV or trastuzumab 600 mg SC using the single-use injection device (Cohort 1) or trastuzumab 600 mg SC (Cohort 2).

Measured Values

	Trastuzumab Subcutaneously and Intravenously
Number of Participants Analyzed	467
Event-free Survival [units: Months] Median (Inter-Quartile Range)	NA (NA to NA) [1]

[1] Event-free survival was not estimated due to the low number of total events and the high percentage of participants who remained censored (> 95% in each cohort) as of the clinical cutoff date of 23 May 2013.

5. Secondary Outcome Measure:

Measure Title	Participant Satisfaction With Subcutaneous Self-administration Using the Single-use Device
Measure Description	Following the crossover period, participants in Cohort 1 who had at least 2 of the total of 18 treatment cycles remaining, were offered the opportunity to self-administer trastuzumab subcutaneously using the single-use injection device under the supervision of a healthcare provider. Of the ≥ 2 treatment cycles remaining, one was used by the healthcare provider to train the patient. Patients were given an evaluation questionnaire after their first self-administration. Participants answered 5 questions using a 5-item rating scale: Strongly disagree, disagree, unsure, agree, strongly agree. Responses to the 5 questions rated their comfort with self-injection, the convenience of the single-use device, their self-confidence using the single-use device, their satisfaction with the single-use device, and whether they would consider using the single-use device again in the future.
Time Frame	Week 24
Safety Issue?	No

Analysis Population Description

Subcutaneous self-administration population: All participants in Cohort 1 who self-administered trastuzumab subcutaneously using the single-use injection device and completed the single-use injection device questionnaire.

Reporting Groups

	Description
Trastuzumab Self-administered Subcutaneously - Cohort 1	Participants in Cohort 1, who had at least 2 treatment cycles remaining of their 18-cycle treatment course, were offered the opportunity to self-administer trastuzumab 600 mg subcutaneously using the single-injection device on Day 1 of each 3-week cycle under the direction of a trained health care practitioner.

Measured Values

	Trastuzumab Self-administered Subcutaneously - Cohort 1
Number of Participants Analyzed	34
Participant Satisfaction With Subcutaneous Self-administration Using the Single-use Device [units: Percentage of participants]	
Comfortable	91.2
Convenient	100.0
Confident	100.0
Satisfied	97.1
Use again	97.1

Reported Adverse Events

Time Frame	[Not specified]
Additional Description	Safety population: All participants who received at least 1 dose of trastuzumab. Not all participants in the safety population received trastuzumab both subcutaneously and intravenously due to participants discontinuing from the study before they crossed-over to the other route of administration.

Reporting Groups

	Description
Trastuzumab SC - Crossover Period	Participants received trastuzumab 600 mg subcutaneously (SC) on Day 1 of each 3-week cycle for 4 cycles.
Trastuzumab IV - Crossover Period	Participants received trastuzumab 6 mg/kg intravenously (IV) on Day 1 of each 3-week cycle for 4 cycles. In case Cycle 1 of the crossover period was the first cycle of trastuzumab treatment, a loading dose of trastuzumab 8 mg/kg IV was administered.

	Description
Trastuzumab IV - Cohort 1 - Continuation Period	Participants received trastuzumab 6 mg/kg intravenous Participants received trastuzumab 6 mg/kg intravenously on Day 1 of each 3-week cycle for up to 10 remaining cycles.
Trastuzumab Self-administered SC - Cohort 1 - Cont	Participants in Cohort 1, who had at least 2 treatment cycles remaining of their 18-cycle treatment course, were offered the opportunity to self-administer trastuzumab 600 mg subcutaneously using the single-injection device on Day 1 of each 3-week cycle under the direction of a trained health care practitioner.
Trastuzumab IV - Cohort 2 - Continuation Period	Participants received trastuzumab 6 mg/kg intravenously on Day 1 of each 3-week cycle for up to 10 remaining cycles.
Trastuzumab SC - Cohort 2 - Continuation Period	Participants received trastuzumab 600 mg/kg subcutaneously on Day 1 of each 3-week cycle for up to 10 remaining cycles.
Cohort 1 - Safety Follow-up Period	Participants were followed for 3 years for safety.
Cohort 2 - Safety Follow-up Period	Participants were followed for 3 years for safety.

Serious Adverse Events

	Trastuzumab SC - Crossover Period	Trastuzumab IV - Crossover Period	Trastuzumab IV - Cohort 1 - Continuation Period	Trastuzumab Self-administered SC - Cohort 1 - Cont	Trastuzumab IV - Cohort 2 - Continuation Period	Trastuzumab SC - Cohort 2 - Continuation Period
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Total	4/479 (0.84%)	2/478 (0.42%)	6/226 (2.65%)	1/42 (2.38%)	0/10 (0%)	4/206 (1.94%)
Cardiac disorders						
Cardiac failure congestive [A] †	0/479 (0%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
General disorders						
Adverse drug reaction [A] †	0/479 (0%)	0/478 (0%)	1/226 (0.44%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Chest pain [A] †	0/479 (0%)	0/478 (0%)	1/226 (0.44%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Hepatobiliary disorders						
Cholelithiasis [A] †	0/479 (0%)	1/478 (0.21%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Infections and infestations						
Breast abscess [A] †	0/479 (0%)	0/478 (0%)	1/226 (0.44%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Device related infection [A] †	1/479 (0.21%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)

	Trastuzumab SC - Crossover Period	Trastuzumab IV - Crossover Period	Trastuzumab IV - Cohort 1 - Continuation Period	Trastuzumab Self-administered SC - Cohort 1 - Cont	Trastuzumab IV - Cohort 2 - Continuation Period	Trastuzumab SC - Cohort 2 - Continuation Period
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Influenza [A] †	0/479 (0%)	1/478 (0.21%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Postoperative wound infection [A] †	0/479 (0%)	0/478 (0%)	1/226 (0.44%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Pyelonephritis [A] †	0/479 (0%)	0/478 (0%)	1/226 (0.44%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Subcutaneous abscess [A] †	1/479 (0.21%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Wound infection [A] †	0/479 (0%)	1/478 (0.21%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	1/206 (0.49%)
Injury, poisoning and procedural complications						
Suture related complication [A] †	0/479 (0%)	1/478 (0.21%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Thermal burn [A] †	0/479 (0%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Adenocarcinoma of colon [A] †	0/479 (0%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Adenoma benign [A] †	1/479 (0.21%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Cerebral haemangioma [A] †	0/479 (0%)	0/478 (0%)	0/226 (0%)	1/42 (2.38%)	0/10 (0%)	0/206 (0%)
Nervous system disorders						
Dizziness [A] †	0/479 (0%)	0/478 (0%)	1/226 (0.44%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Psychiatric disorders						
Mental disorder [A] †	0/479 (0%)	1/478 (0.21%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Reproductive system and breast disorders						
Endometrial hypertrophy [A] †	0/479 (0%)	0/478 (0%)	1/226 (0.44%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Surgical and medical procedures						
Breast reconstruction [A] †	0/479 (0%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	1/206 (0.49%)

	Trastuzumab SC - Crossover Period	Trastuzumab IV - Crossover Period	Trastuzumab IV - Cohort 1 - Continuation Period	Trastuzumab Self-administered SC - Cohort 1 - Cont	Trastuzumab IV - Cohort 2 - Continuation Period	Trastuzumab SC - Cohort 2 - Continuation Period
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Knee arthroplasty [A] †	0/479 (0%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	1/206 (0.49%)
Mammoplasty [A] †	0/479 (0%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	1/206 (0.49%)
Synovectomy [A] †	0/479 (0%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Vascular disorders						
Haematoma [A] †	1/479 (0.21%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)
Venous thrombosis limb [A] †	0/479 (0%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	0/206 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (16.0)

	Cohort 1 - Safety Follow-up Period	Cohort 2 - Safety Follow-up Period
	Affected/At Risk (%)	Affected/At Risk (%)
Total	5/248 (2.02%)	1/153 (0.65%)
Cardiac disorders		
Cardiac failure congestive [A] †	0/248 (0%)	1/153 (0.65%)
General disorders		
Adverse drug reaction [A] †	0/248 (0%)	0/153 (0%)
Chest pain [A] †	0/248 (0%)	0/153 (0%)
Hepatobiliary disorders		
Cholelithiasis [A] †	0/248 (0%)	0/153 (0%)
Infections and infestations		
Breast abscess [A] †	0/248 (0%)	0/153 (0%)
Device related infection [A] †	0/248 (0%)	0/153 (0%)

	Cohort 1 - Safety Follow-up Period	Cohort 2 - Safety Follow-up Period
	Affected/At Risk (%)	Affected/At Risk (%)
Influenza [A] †	0/248 (0%)	0/153 (0%)
Postoperative wound infection [A] †	0/248 (0%)	0/153 (0%)
Pyelonephritis [A] †	0/248 (0%)	0/153 (0%)
Subcutaneous abscess [A] †	0/248 (0%)	0/153 (0%)
Wound infection [A] †	0/248 (0%)	0/153 (0%)
Injury, poisoning and procedural complications		
Suture related complication [A] †	0/248 (0%)	0/153 (0%)
Thermal burn [A] †	1/248 (0.4%)	0/153 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Adenocarcinoma of colon [A] †	1/248 (0.4%)	0/153 (0%)
Adenoma benign [A] †	0/248 (0%)	0/153 (0%)
Cerebral haemangioma [A] †	0/248 (0%)	0/153 (0%)
Nervous system disorders		
Dizziness [A] †	0/248 (0%)	0/153 (0%)
Psychiatric disorders		
Mental disorder [A] †	0/248 (0%)	0/153 (0%)
Reproductive system and breast disorders		
Endometrial hypertrophy [A] †	0/248 (0%)	0/153 (0%)
Surgical and medical procedures		
Breast reconstruction [A] †	1/248 (0.4%)	0/153 (0%)
Knee arthroplasty [A] †	0/248 (0%)	0/153 (0%)
Mammoplasty [A] †	0/248 (0%)	0/153 (0%)
Synovectomy [A] †	1/248 (0.4%)	0/153 (0%)

	Cohort 1 - Safety Follow-up Period	Cohort 2 - Safety Follow-up Period
	Affected/At Risk (%)	Affected/At Risk (%)
Vascular disorders		
Haematoma [A] †	0/248 (0%)	0/153 (0%)
Venous thrombosis limb [A] †	1/248 (0.4%)	0/153 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (16.0)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Trastuzumab SC - Crossover Period	Trastuzumab IV - Crossover Period	Trastuzumab IV - Cohort 1 - Continuation Period	Trastuzumab Self-administered SC - Cohort 1 - Cont	Trastuzumab IV - Cohort 2 - Continuation Period	Trastuzumab SC - Cohort 2 - Continuation Period
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Total	80/479 (16.7%)	31/478 (6.49%)	22/226 (9.73%)	3/42 (7.14%)	0/10 (0%)	26/206 (12.62%)
Gastrointestinal disorders						
Nausea [A] †	25/479 (5.22%)	14/478 (2.93%)	5/226 (2.21%)	1/42 (2.38%)	0/10 (0%)	2/206 (0.97%)
General disorders						
Asthenia [A] †	27/479 (5.64%)	23/478 (4.81%)	6/226 (2.65%)	0/42 (0%)	0/10 (0%)	6/206 (2.91%)
Injection site erythema [A] †	27/479 (5.64%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	3/206 (1.46%)
Injection site pain [A] †	32/479 (6.68%)	0/478 (0%)	0/226 (0%)	2/42 (4.76%)	0/10 (0%)	5/206 (2.43%)
Injection site reaction [A] †	30/479 (6.26%)	0/478 (0%)	0/226 (0%)	0/42 (0%)	0/10 (0%)	3/206 (1.46%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A] †	24/479 (5.01%)	27/478 (5.65%)	11/226 (4.87%)	0/42 (0%)	0/10 (0%)	7/206 (3.4%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (16.0)

	Cohort 1 - Safety Follow-up Period	Cohort 2 - Safety Follow-up Period
	Affected/At Risk (%)	Affected/At Risk (%)
Total	0/248 (0%)	0/153 (0%)
Gastrointestinal disorders		
Nausea [A] †	0/248 (0%)	0/153 (0%)
General disorders		
Asthenia [A] †	0/248 (0%)	0/153 (0%)
Injection site erythema [A] †	0/248 (0%)	0/153 (0%)
Injection site pain [A] †	0/248 (0%)	0/153 (0%)
Injection site reaction [A] †	0/248 (0%)	0/153 (0%)
Musculoskeletal and connective tissue disorders		
Arthralgia [A] †	0/248 (0%)	0/153 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (16.0)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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