Clinical trial results:
National Phase IIIb Prospective Two-Cohort Non-Randomized, Multi-centre, Open Label Study to Assess the Safety of Subcutaneous Trastuzumab and Molecular Biomarkers in Patients with Early and Locally Advanced HER2-Positive Breast Cancer

Summary

EudraCT number	2013-001161-16
Trial protocol	IT
Global end of trial date	27 March 2018

Results information

Result version number	v3
This version publication date	20 February 2020
First version publication date	28 May 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	ML28879

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01940497
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche, Ltd.
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, 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	27 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2016
Global end of trial reached?	Yes
Global end of trial date	27 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the safety and tolerability of trastuzumab solution injected subcutaneously (vial or single-use injection device [SID]) in participants with human epidermal growth factor receptor 2 (HER2)-positive early or locally-advanced breast cancer.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 240
Worldwide total number of subjects	240
EEA total number of subjects	240

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)	197
From 65 to 84 years	43

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of 263 screened participants, 240 participants were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab (Vial)

Arm description:

Participants received trastuzumab 600 milligrams (mg) subcutaneously using a vial every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant or neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).

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

Dosage and administration details:

Participants received trastuzumab 600 mg subcutaneously every 3 weeks (1 cycle) for 18 cycles.

Arm title	Trastuzumab (SID)

Arm description:

Participants received trastuzumab 600 mg subcutaneously using SID every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant or neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).

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

Dosage and administration details:

Participants received trastuzumab 600 mg subcutaneously every 3 weeks (1 cycle) for 18 cycles.

Number of subjects in period 1	Trastuzumab (Vial)	Trastuzumab (SID)
Started	121	119
Treated	115	113
Completed	1	1
Not completed	120	118
Adverse event/Intercurrent illness	1	-
Consent withdrawn by subject	2	-
Failure to return	-	1
Ongoing at data cut-off	116	117
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Trastuzumab (Vial)
Reporting group description:	
Participants received trastuzumab 600 milligrams (mg) subcutaneously using a vial every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant or neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Reporting group title	Trastuzumab (SID)
Reporting group description:	
Participants received trastuzumab 600 mg subcutaneously using SID every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant or neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	

Reporting group values	Trastuzumab (Vial)	Trastuzumab (SID)	Total
Number of subjects	121	119	240
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)	94	103	197
From 65-84 years	27	16	43
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	55.1	53.2	
standard deviation	± 10.51	± 10.37	-
Gender Categorical Units: Subjects			
Female	120	119	239
Male	1	0	1

End points

End points reporting groups

Reporting group title	Trastuzumab (Vial)
Reporting group description:	
Participants received trastuzumab 600 milligrams (mg) subcutaneously using a vial every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant or neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Reporting group title	Trastuzumab (SID)
Reporting group description:	
Participants received trastuzumab 600 mg subcutaneously using SID every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant or neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Subject analysis set title	Trastuzumab (Vial): Adjuvant
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received trastuzumab 600 mg subcutaneously using a vial every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Subject analysis set title	Trastuzumab (Vial): Neoadjuvant
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received trastuzumab 600 mg subcutaneously using a vial every 3 weeks (1 cycle) for 1 year (4 cycles in combination with neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Subject analysis set title	Trastuzumab (SID): Adjuvant
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received trastuzumab 600 mg subcutaneously using SID every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Subject analysis set title	Trastuzumab (SID): Neoadjuvant
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received trastuzumab 600 mg subcutaneously using SID every 3 weeks (1 cycle) for 1 year (4 cycles in combination with neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Subject analysis set title	Trastuzumab (Vial): Adjuvant
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received trastuzumab 600 mg subcutaneously using a vial every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Subject analysis set title	Trastuzumab (Vial): Neoadjuvant
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received trastuzumab 600 mg subcutaneously using a vial every 3 weeks (1 cycle) for 1 year (4 cycles in combination with neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Subject analysis set title	Trastuzumab (SID): Adjuvant
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants received trastuzumab 600 mg subcutaneously using SID every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Subject analysis set title	Trastuzumab (SID): Neoadjuvant

Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received trastuzumab 600 mg subcutaneously using SID every 3 weeks (1 cycle) for 1 year (4 cycles in combination with neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).

Subject analysis set title	HCPs: Trastuzumab (Vial)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received trastuzumab 600 mg subcutaneously using a vial every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant or neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone). Trastuzumab using vial had to be administered by an HCP. Such HCPs were included in this group.

Subject analysis set title	HCPs: Trastuzumab (SID)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received trastuzumab 600 mg subcutaneously using SID every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant or neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone). Trastuzumab using SID had to be administered by an HCP or by the participant after appropriate training and under HCP supervision. Such HCPs were included in this group.

Primary: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. TEAEs were the AEs occurring from starting on the day of or after first administration of trastuzumab and within 28 days after last dose of trastuzumab. Data for this outcome measure were analyzed and reported by adjuvant versus neo-adjuvant chemotherapy groups within each treatment arm. Safety population included all enrolled participants who received at least one dose of study medication. Data for this outcome measure were analyzed and reported by adjuvant versus neoadjuvant chemotherapy groups within each treatment arm.

End point type	Primary

End point timeframe:

Day 1 up to 28 days after last dose of trastuzumab (up to approximately 1 year)

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: This endpoint is descriptive only, there is no formal comparison between arms and statistical analysis

End point values	Trastuzumab (Vial): Adjuvant	Trastuzumab (Vial): Neoadjuvant	Trastuzumab (SID): Adjuvant	Trastuzumab (SID): Neoadjuvant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	95	20	92	21
Units: percentage of participants				
number (not applicable)	98.9	100.0	89.1	95.2

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Dose of Trastuzumab Administered

End point title	Actual Dose of Trastuzumab Administered

End point description:

Actual dose (mg) administered = (sum over all cycles of actual dose received [mg] divided by number of cycles). Safety population. Data for this outcome measure were analyzed and reported by adjuvant versus neoadjuvant chemotherapy groups within each treatment arm.

End point type	Secondary

End point timeframe:

Day 1 up last dose of trastuzumab (up to approximately 1 year)

End point values	Trastuzumab (Vial): Adjuvant	Trastuzumab (Vial): Neoadjuvant	Trastuzumab (SID): Adjuvant	Trastuzumab (SID): Neoadjuvant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	95	20	92	21
Units: mg				
arithmetic mean (standard deviation)	599.7 (± 3.08)	600.00 (± 0.000)	593.3 (± 16.55)	595.9 (± 10.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Treatment with Trastuzumab

End point title	Duration of Treatment with Trastuzumab

End point description:

Safety population. Data for this outcome measure were analyzed and reported by adjuvant versus neoadjuvant chemotherapy groups within each treatment arm.

End point type	Secondary

End point timeframe:

Day 1 up last dose of trastuzumab (up to approximately 1 year)

End point values	Trastuzumab (Vial): Adjuvant	Trastuzumab (Vial): Neoadjuvant	Trastuzumab (SID): Adjuvant	Trastuzumab (SID): Neoadjuvant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	95	20	92	21
Units: days				
arithmetic mean (standard deviation)	346 (± 72.13)	352.2 (± 55.82)	340.1 (± 85.47)	351.9 (± 90.02)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Received Concomitant Medications

End point title	Percentage of Participants Who Received Concomitant Medications

End point description:

Safety population.

End point type	Secondary

End point timeframe:

Screening (Day -28 to -1) up to approximately 2.5 years (assessed up to cut off date 05 April 2016)

End point values	Trastuzumab (Vial)	Trastuzumab (SID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	113		
Units: percentage of participants				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Pathological Complete Response (pCR) (Neoadjuvant Groups Only) Using Mammography

End point title	Percentage of Participants with Pathological Complete Response (pCR) (Neoadjuvant Groups Only) Using Mammography

End point description:

In the neoadjuvant setting, the activity of two sequential drug regimens, doxorubicin-containing chemotherapy followed by paclitaxel or docetaxel chemotherapy in combination with trastuzumab, was assessed as the percentage of participants with pCR in breast and nodes using mammography. pCR was defined as the absence of histological evidence of invasive breast cancer cells in the tissue specimen removed from the breast after preoperative treatment. Modified intent-to-treat (mITT) population included all enrolled participants satisfying criteria for eligibility. Data for this outcome measure were analyzed and reported only for neoadjuvant groups within each treatment arm.

End point type	Secondary

End point timeframe:

Day 1 up to 24 weeks

End point values	Trastuzumab (Vial): Neoadjuvant	Trastuzumab (SID): Neoadjuvant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	19		
Units: percentage of participants				
number (confidence interval 95%)	40.9 (31.0 to 51.0)	15.8 (8.00 to 24.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Event (Local, Regional or Distant Recurrence, Contralateral Breast Cancer or Death) Using Mammography

End point title	Percentage of Participants with Event (Local, Regional or Distant Recurrence, Contralateral Breast Cancer or Death) Using Mammography

End point description:

A participant was considered as disease free if the participant was free from local, regional or distant recurrence, contralateral breast cancer or death due to any cause (whichever occurred first). Percentage of participants with event at the cut off date were reported. m-ITT population. Here, 'Number of Subjects Analysed' = participants who were evaluable for this outcome measure. Data for this outcome measure were analyzed and reported by adjuvant versus neoadjuvant chemotherapy groups within each treatment arm.

End point type	Secondary

End point timeframe:

Day 1 up to local, regional or distant recurrence, contralateral breast cancer or death due to any cause (whichever occurred first; up to 5 years)

End point values	Trastuzumab (Vial): Adjuvant	Trastuzumab (Vial): Neoadjuvant	Trastuzumab (SID): Adjuvant	Trastuzumab (SID): Neoadjuvant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	92	18	91	18
Units: percentage of participants				
number (not applicable)	18.5	33.3	6.6	11.1

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS) Using Mammography

End point title	Disease-Free Survival (DFS) Using Mammography

End point description:

DFS was defined as the time from the first treatment to local, regional or distant recurrence, contralateral breast cancer or death due to any cause (whichever occurred first). Kaplan-Meier estimates were used for analysis. Participants who were disease-free were censored at the data cut off date. m-ITT population. Here, 'Number of Subjects Analysed' = participants who were evaluable for this outcome measure. Data for this outcome measure were analyzed and reported by adjuvant versus neoadjuvant chemotherapy groups within each treatment arm. Here, '99999' indicates that median and corresponding 95% confidence interval (CI) could not be estimated because majority of participants were censored at data cut off date.

End point type	Secondary

End point timeframe:

Day 1 up to local, regional or distant recurrence, contralateral breast cancer or death due to any cause (whichever occurred first; up to 5 years)

End point values	Trastuzumab (Vial): Adjuvant	Trastuzumab (Vial): Neoadjuvant	Trastuzumab (SID): Adjuvant	Trastuzumab (SID): Neoadjuvant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	92	18	91	18
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

m-ITT population. Data for this outcome measure were analyzed and reported by adjuvant versus neoadjuvant chemotherapy groups within each treatment arm.

End point type	Secondary

End point timeframe:

Day 1 up to death due to any cause (up to 5 years)

End point values	Trastuzumab (Vial): Adjuvant	Trastuzumab (Vial): Neoadjuvant	Trastuzumab (SID): Adjuvant	Trastuzumab (SID): Neoadjuvant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	96	22	93	19
Units: percentage of participants				
number (not applicable)	5.2	4.5	0.0	5.26

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time from the first treatment to death from any cause. Kaplan-Meier estimates were used for analysis. Participants who did not die were censored on the date they were last known to be alive. m-ITT population. Data for this outcome measure were analyzed and reported by

adjuvant versus neoadjuvant chemotherapy groups within each treatment arm. Here, '99999' indicates that median and corresponding 95% CI could not be estimated because majority of participants were censored at data cut off date.

End point type	Secondary

End point timeframe:

Day 1 up to death due to any cause (up to 5 years)

End point values	Trastuzumab (Vial): Adjuvant	Trastuzumab (Vial): Neoadjuvant	Trastuzumab (SID): Adjuvant	Trastuzumab (SID): Neoadjuvant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	96	22	93	19
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Response to Patient Satisfaction Questionnaire (PSQ)

End point title	Percentage of Participants by Response to Patient Satisfaction Questionnaire (PSQ)[2]

End point description:

Participants were asked following 5 questions:(1)"Following first injection given by physician/nurse and training on SID, I felt comfortable injecting it by myself";(2)" SID was convenient and easy to use";(3)"I am confident giving myself injection in thigh with SID";(4)"Taking all things into account, I find self-administration using SID satisfactory";(5)"If given opportunity, I would choose to continue self-injection using SID at home". Responses were recorded as:"Unknown","Strongly Disagree","Disagree","Unsure","Agree","Strongly Agree".Percentage of participants providing responses was reported. PSQ population included all enrolled participants from SID group who were able to use SID and had completed a minimum 14 administrations subcutaneously using SID (at least 10 of which were self-administered). Here, 'Number of Subjects Analysed' = participants who were evaluable for this outcome measure.Data for this outcome measure were analyzed and reported only for SID arm.

End point type	Secondary

End point timeframe:

After at least 14 cycles (1 cycle = 21 days; maximum up to 1 year)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is descriptive only, no statistic is required. The questionnaire was administered in certain circumstances only.

End point values	Trastuzumab (SID)			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: percentage of participants				
number (not applicable)				
Comfortable: Unknown	0.0			
Comfortable: Strongly Disagree	0.0			

Comfortable: Disagree	0.0			
Comfortable: Unsure	6.7			
Comfortable: Agree	40			
Comfortable: Strongly Agree	53.3			
Convenient: Unknown	0.0			
Convenient: Strongly Disagree	0.0			
Convenient: Disagree	0.0			
Convenient: Unsure	6.7			
Convenient: Agree	33.3			
Convenient: Strongly Agree	60			
Confident: Unknown	0.0			
Confident: Strongly Disagree	0.0			
Confident: Disagree	0.0			
Confident: Unsure	6.7			
Confident: Agree	40			
Confident: Strongly Agree	53.3			
Satisfactory: Unknown	0.0			
Satisfactory: Strongly Disagree	0.0			
Satisfactory: Disagree	0.0			
Satisfactory: Unsure	6.7			
Satisfactory: Agree	33.3			
Satisfactory: Strongly Agree	60			
Would continue: Unknown	0.0			
Would continue: Strongly Disagree	0.0			
Would continue: Disagree	13.3			
Would continue: Unsure	6.7			
Would continue: Agree	20			
Would continue: Strongly Agree	60			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Health Care Professionals (HCPs) by Response to Health Care Professional Questionnaire (HCPQ)

End point title	Percentage of Health Care Professionals (HCPs) by Response to Health Care Professional Questionnaire (HCPQ)

End point description:

Percentage of HCPs providing responses to various questions related to overall ease of study drug administration was reported in different categories, where categories indicate all possible responses to such questions. HCPQ population included all investigators and study nurses who completed the questionnaire at each site when at least 4 participants from their site had received at least 5 cycles of adjuvant study treatment. Here, '9999' indicates that data were not evaluable as the question applied only to vial group; and '999999' indicates that data were not evaluable as the question applied only to SID group.

End point type	Secondary

End point timeframe:

After at least 4 participants completed 5 cycles of adjuvant treatment (1 cycle = 21 days; maximum up to 1 year)

End point values	HCPs: Trastuzumab (Vial)	HCPs: Trastuzumab (SID)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121[3]	119[4]		
Units: percentage of health care professionals				
number (not applicable)				
Specialization: Oncologist	17.3	16.0		
Specialization: Specialist nurse	69.2	76.0		
Specialization: Other	11.5	8.0		
Specialization: Missing	1.9	0.0		
Personally administered/supervised: Always	40.4	48.0		
Personally administered/supervised: Sometimes	51.9	48.0		
Personally administered/supervised: Never	7.7	4.0		
If 'Never', who administered: Specialist nurse	7.7	4.0		
Syringe prepared at: Pharmacy	55.8	9999		
Syringe prepared at: Oncology ward	40.4	9999		
Syringe prepared at: Missing	3.8	9999		
Time to fill syringe: less than (<) 5 minutes	67.3	9999		
Time to fill syringe: 6-10 minutes	13.5	9999		
Time to fill syringe: 11-15 minutes	5.8	9999		
Time to fill syringe: Unknown	13.5	9999		
Total time for vial administration: <3 minutes	1.9	9999		
Total time for vial administration: <5 minutes	59.6	9999		
Total time for vial administration: 6-15 minutes	38.5	9999		
Time to prepare SID: <5 minutes	999999	72.0		
Time to prepare SID: 6-10 minutes	999999	14.0		
Time to prepare SID: 11-15 minutes	999999	4.0		
Time to prepare SID: 16-20 minutes	999999	2.0		
Time to prepare SID: >20 minutes	999999	8.0		
Total time for SID administration: <3 minutes	999999	26.0		
Total time for SID administration: <5 minutes	999999	30.0		
Total time for SID administration: 6-15 minutes	999999	44.0		
Injection site: Irritation: A lot	1.9	4.0		
Injection site: Irritation: A few	46.2	36.0		
Injection site: Irritation: None	51.9	60.0		
Injection site: Bruising: A few	7.7	10.0		
Injection site: Bruising: None	92.3	90.0		
Injection site: Infection: None	100.0	100.0		
Fever,shivering,flu-like,rash,swelling:A few	15.4	14.0		

Fever,shivering,flu-like,rash,swelling:None	84.6	86.0		
Time at hospital for administration: <2 hours	44.2	44.0		
Time at hospital for administration: >2, <3 hours	23.1	34.0		
Time at hospital for administration: >3, <4 hours	23.1	12.0		
Time at hospital for administration: >4 hours	7.7	10.0		
Time at hospital for administration: Missing	1.9	0.0		
Anxiety to participants: None	82.7	90.0		
Anxiety to participants: A fair amount	17.3	10.0		
Ease of vial administration: None	5.8	9999		
Ease of vial administration: A fair amount	38.5	9999		
Ease of vial administration: A lot	55.8	9999		
Subcutaneous route may simplify management: Yes	94.2	100.0		
Subcutaneous route may simplify management: No	5.8	0.0		
Would recommend SID to intravenous route: Yes	96.2	96.0		
Would recommend SID to intravenous route: No	3.8	4.0		
Would recommend subcutaneous route to medics: Yes	100.0	90.0		
Would recommend subcutaneous route to medics: No	0.0	8.0		
Would recommend subcutaneous to medics:Missing	0.0	2.0		
Convenience of using SID by participants: Yes	94.2	96.0		
Convenience of using SID by participants: No	0.0	4.0		
Convenience of using SID by participants: Yes/No	5.8	0.0		

Notes:

[3] - Total 52 health care professionals were analyzed.

[4] - Total 50 health care professionals were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to 28 days after last dose of trastuzumab (up to approximately 1 year)	
Adverse event reporting additional description:	
Safety population TEAEs	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Trastuzumab (Vial)
Reporting group description:	
Participants received trastuzumab 600 milligrams (mg) subcutaneously using a vial every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant or neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	
Reporting group title	Trastuzumab (SID)
Reporting group description:	
Participants received trastuzumab 600 mg subcutaneously using SID every 3 weeks (1 cycle) for 1 year (4 cycles in combination with adjuvant or neoadjuvant chemotherapy [consisting of doxorubicin, paclitaxel or docetaxel] and 14 cycles administered alone).	

Serious adverse events	Trastuzumab (Vial)	Trastuzumab (SID)	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 115 (6.96%)	9 / 113 (7.96%)	
number of deaths (all causes)	6	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 115 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian epithelial cancer metastatic			

subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 115 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuropericarditis			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 115 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 115 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pryexia			
subjects affected / exposed	0 / 115 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 115 (0.87%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 115 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Generalised anxiety disorder			
subjects affected / exposed	0 / 115 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 115 (0.00%)	1 / 113 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			

subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trastuzumab (Vial)	Trastuzumab (SID)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 115 (97.39%)	97 / 113 (85.84%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	12 / 115 (10.43%)	9 / 113 (7.96%)	
occurrences (all)	12	9	
Hypertension			
subjects affected / exposed	12 / 115 (10.43%)	9 / 113 (7.96%)	
occurrences (all)	12	10	
Lymphoedema			
subjects affected / exposed	6 / 115 (5.22%)	2 / 113 (1.77%)	
occurrences (all)	6	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	35 / 115 (30.43%)	27 / 113 (23.89%)	
occurrences (all)	55	36	
Pyrexia			
subjects affected / exposed	22 / 115 (19.13%)	17 / 113 (15.04%)	
occurrences (all)	36	20	
Fatigue			
subjects affected / exposed	12 / 115 (10.43%)	13 / 113 (11.50%)	
occurrences (all)	18	22	
Oedema peripheral			

subjects affected / exposed	10 / 115 (8.70%)	12 / 113 (10.62%)	
occurrences (all)	11	17	
Mucosal inflammation			
subjects affected / exposed	9 / 115 (7.83%)	8 / 113 (7.08%)	
occurrences (all)	9	11	
Chest pain			
subjects affected / exposed	7 / 115 (6.09%)	1 / 113 (0.88%)	
occurrences (all)	7	1	
Pain			
subjects affected / exposed	7 / 115 (6.09%)	4 / 113 (3.54%)	
occurrences (all)	8	5	
Influenza like illness			
subjects affected / exposed	6 / 115 (5.22%)	3 / 113 (2.65%)	
occurrences (all)	6	3	
Oedema			
subjects affected / exposed	6 / 115 (5.22%)	2 / 113 (1.77%)	
occurrences (all)	6	2	
Injection site erythema			
subjects affected / exposed	2 / 115 (1.74%)	1 / 113 (0.88%)	
occurrences (all)	2	1	
Peripheral swelling			
subjects affected / exposed	1 / 115 (0.87%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	5 / 115 (4.35%)	0 / 113 (0.00%)	
occurrences (all)	5	0	
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	4 / 115 (3.48%)	5 / 113 (4.42%)	
occurrences (all)	4	5	
Menopausal symptoms			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	15 / 115 (13.04%)	16 / 113 (14.16%)	
occurrences (all)	16	18	
Epistaxis			
subjects affected / exposed	14 / 115 (12.17%)	10 / 113 (8.85%)	
occurrences (all)	18	10	
Dyyspnoea			
subjects affected / exposed	5 / 115 (4.35%)	5 / 113 (4.42%)	
occurrences (all)	7	5	
Oropharyngeal pain			
subjects affected / exposed	4 / 115 (3.48%)	1 / 113 (0.88%)	
occurrences (all)	5	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 115 (4.35%)	5 / 113 (4.42%)	
occurrences (all)	5	5	
Panic attack			
subjects affected / exposed	2 / 115 (1.74%)	0 / 113 (0.00%)	
occurrences (all)	2	0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	15 / 115 (13.04%)	6 / 113 (5.31%)	
occurrences (all)	15	6	
Neutrophil count decreased			
subjects affected / exposed	3 / 115 (2.61%)	8 / 113 (7.08%)	
occurrences (all)	9	10	
White blood cell count decreased			
subjects affected / exposed	2 / 115 (1.74%)	6 / 113 (5.31%)	
occurrences (all)	4	11	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 115 (2.61%)	4 / 113 (3.54%)	
occurrences (all)	3	6	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 115 (0.87%)	2 / 113 (1.77%)	
occurrences (all)	1	2	
Blood pressure increased			

subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Hepatitis C virus test positive			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	2 / 115 (1.74%)	5 / 113 (4.42%)	
occurrences (all)	2	5	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	3 / 115 (2.61%)	2 / 113 (1.77%)	
occurrences (all)	3	2	
Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	2 / 115 (1.74%)	2 / 113 (1.77%)	
occurrences (all)	2	2	
Tachycardia			
subjects affected / exposed	6 / 115 (5.22%)	3 / 113 (2.65%)	
occurrences (all)	6	5	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	52 / 115 (45.22%)	28 / 113 (24.78%)	
occurrences (all)	78	34	
Headache			
subjects affected / exposed	8 / 115 (6.96%)	5 / 113 (4.42%)	
occurrences (all)	9	5	
Dysgeusia			
subjects affected / exposed	6 / 115 (5.22%)	7 / 113 (6.19%)	
occurrences (all)	6	7	
Neurotoxicity			
subjects affected / exposed	6 / 115 (5.22%)	6 / 113 (5.31%)	
occurrences (all)	10	6	
Dizziness			

subjects affected / exposed	5 / 115 (4.35%)	2 / 113 (1.77%)	
occurrences (all)	6	2	
Neuropathy peripheral			
subjects affected / exposed	5 / 115 (4.35%)	3 / 113 (2.65%)	
occurrences (all)	6	3	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 115 (1.74%)	0 / 113 (0.00%)	
occurrences (all)	2	0	
Presyncope			
subjects affected / exposed	3 / 115 (2.61%)	2 / 113 (1.77%)	
occurrences (all)	3	3	
Sciatica			
subjects affected / exposed	5 / 115 (4.35%)	1 / 113 (0.88%)	
occurrences (all)	7	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	24 / 115 (20.87%)	4 / 113 (3.54%)	
occurrences (all)	38	4	
Anaemia			
subjects affected / exposed	17 / 115 (14.78%)	11 / 113 (9.73%)	
occurrences (all)	19	12	
Leukopenia			
subjects affected / exposed	13 / 115 (11.30%)	6 / 113 (5.31%)	
occurrences (all)	19	7	
Eye disorders			
Eye disorder			
subjects affected / exposed	2 / 115 (1.74%)	0 / 113 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	28 / 115 (24.35%)	21 / 113 (18.58%)	
occurrences (all)	51	23	
Nausea			
subjects affected / exposed	10 / 115 (8.70%)	16 / 113 (14.16%)	
occurrences (all)	19	19	
Stomatitis			

subjects affected / exposed	9 / 115 (7.83%)	10 / 113 (8.85%)	
occurrences (all)	12	11	
Abdominal pain upper			
subjects affected / exposed	9 / 115 (7.83%)	5 / 113 (4.42%)	
occurrences (all)	10	5	
Constipation			
subjects affected / exposed	8 / 115 (6.96%)	7 / 113 (6.19%)	
occurrences (all)	10	7	
Vomiting			
subjects affected / exposed	7 / 115 (6.09%)	7 / 113 (6.19%)	
occurrences (all)	7	9	
Abdominal pain			
subjects affected / exposed	6 / 115 (5.22%)	3 / 113 (2.65%)	
occurrences (all)	7	3	
Dyspepsia			
subjects affected / exposed	6 / 115 (5.22%)	4 / 113 (3.54%)	
occurrences (all)	10	4	
Haemorrhoids			
subjects affected / exposed	2 / 115 (1.74%)	5 / 113 (4.42%)	
occurrences (all)	2	6	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	25 / 115 (21.74%)	16 / 113 (14.16%)	
occurrences (all)	30	17	
Nail disorder			
subjects affected / exposed	13 / 115 (11.30%)	9 / 113 (7.96%)	
occurrences (all)	13	9	
Nail ridging			
subjects affected / exposed	7 / 115 (6.09%)	1 / 113 (0.88%)	
occurrences (all)	7	1	
Pruritus			
subjects affected / exposed	7 / 115 (6.09%)	7 / 113 (6.19%)	
occurrences (all)	7	7	
Rash			
subjects affected / exposed	6 / 115 (5.22%)	7 / 113 (6.19%)	
occurrences (all)	6	8	

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 115 (0.87%)	1 / 113 (0.88%)	
occurrences (all)	1	1	
Skin disorder			
subjects affected / exposed	3 / 115 (2.61%)	2 / 113 (1.77%)	
occurrences (all)	3	2	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	4 / 115 (3.48%)	4 / 113 (3.54%)	
occurrences (all)	4	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	33 / 115 (28.70%)	33 / 113 (29.20%)	
occurrences (all)	40	39	
Myalgia			
subjects affected / exposed	13 / 115 (11.30%)	10 / 113 (8.85%)	
occurrences (all)	14	14	
Back Pain			
subjects affected / exposed	11 / 115 (9.57%)	7 / 113 (6.19%)	
occurrences (all)	12	8	
Pain in extremity			
subjects affected / exposed	9 / 115 (7.83%)	4 / 113 (3.54%)	
occurrences (all)	9	5	
Musculoskeletal pain			
subjects affected / exposed	7 / 115 (6.09%)	9 / 113 (7.96%)	
occurrences (all)	9	9	
Bone pain			
subjects affected / exposed	4 / 115 (3.48%)	5 / 113 (4.42%)	
occurrences (all)	8	7	
Joint stiffness			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Osteopenia			
subjects affected / exposed	4 / 115 (3.48%)	2 / 113 (1.77%)	
occurrences (all)	4	2	
Osteoporosis			

subjects affected / exposed	5 / 115 (4.35%)	3 / 113 (2.65%)	
occurrences (all)	5	3	
Infections and infestations			
Cystitis			
subjects affected / exposed	7 / 115 (6.09%)	9 / 113 (7.96%)	
occurrences (all)	12	11	
Influenza			
subjects affected / exposed	4 / 115 (3.48%)	12 / 113 (10.62%)	
occurrences (all)	4	13	
Conjunctivitis			
subjects affected / exposed	5 / 115 (4.35%)	4 / 113 (3.54%)	
occurrences (all)	6	4	
Mastitis			
subjects affected / exposed	3 / 115 (2.61%)	1 / 113 (0.88%)	
occurrences (all)	4	1	
Pharyngitis			
subjects affected / exposed	5 / 115 (4.35%)	5 / 113 (4.42%)	
occurrences (all)	5	5	
Postoperative wound infection			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 115 (2.61%)	6 / 113 (5.31%)	
occurrences (all)	5	8	
Hypophagia			
subjects affected / exposed	1 / 115 (0.87%)	0 / 113 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2014	- Modifications were done in eligibility criteria. - For the purpose of fertility preservation (adjuvant participants only), luteinizing hormone-releasing hormone analogous administration was allowed without limitation. - Clarification was added on the time points for mammography, radiological examinations, and centralized analysis of tissue and blood samples at baseline, and on the process of left ventricular ejection fraction (LVEF) assessments. - An additional blood pressure assessment was included after study drug administration. - Allowed contraception was updated to align with exclusion criteria. - Timelines and procedures to assess breast cancer at screening was added to the Schedule of Assessments to align with the text in the protocol. - The lowest dose of docetaxel (75 milligrams per square meter [mg/m^2]) was to be permitted because it is routine medical practice.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported