Clinical trial results:
An Open-Label, Randomized, Multicenter Phase Iii Study In Patients With Her2-Positive Metastatic Breast Cancer Responding To First Line Treatment With Intravenous Trastuzumab For At Least 3 Years And Investigating Patient Preference For Subcutaneous Trastuzumab

Summary

EudraCT number	2012-003442-32
Trial protocol	FR
Global end of trial date	17 July 2019

Results information

Result version number	v1 (current)
This version publication date	01 August 2020
First version publication date	01 August 2020

Trial information

Trial identification

Sponsor protocol code	ML28589

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01810393
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Hoffmann-La Roche, Medical Communications, +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	04 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This open-label, randomized, multicenter study evaluated subjects preference for subcutaneous (SC) versus intravenous (IV) trastuzumab (Herceptin) in subjects with HER2-positive metastatic breast cancer responding to first-line treatment with IV trastuzumab for at least 3 years. Subjects were randomized to receive either 3 cycles (cycle length = 21 days) of trastuzumab SC followed by 3 cycles of trastuzumab IV or 3 cycles of trastuzumab IV followed by 3 cycles of trastuzumab SC. All subjects received trastuzumab SC for Cycles 7 to 18.

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following:
● Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
● Applicable ICH Good Clinical Practice (GCP) Guidelines
● Applicable laws and regulations

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2013
Long term follow-up planned	Yes
Long term follow-up rationale	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	France: 114
Worldwide total number of subjects	114
EEA total number of subjects	114

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)	81
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening period: within 21 days prior to study treatment start (Baseline visit, Day 1), subjects eligibility was determined at the Screening visit. At Baseline visit, patient's inclusion in the study was established.

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	Trastuzumab SC then IV

Arm description:

Subjects received treatment with Trastuzumab IV for the first 3 cycles (cycle length = 21 days) followed by Trastuzumab SC for the next 3 cycles. Subjects continued receiving treatment with trastuzumab SC for another 12 cycles (if SC treatment is well tolerated, otherwise subjects continued IV treatment) for a total of 18 cycles of treatment during the study.

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

Dosage and administration details:

Trastuzumab was administered at a dose of 600 milligrams per 5 milliliter (mg/5mL) SC in 21-day cycles as per schedule described in respective arm.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered at a dose of 6 milligrams per kilogram (mg/kg) IV in 21-day cycles as per schedule described in respective arm.

Arm title	Trastuzumab IV then SC

Arm description:

Subjects received treatment with Trastuzumab SC for the first 3 cycles (cycle length = 21 days) followed by Trastuzumab IV for the next 3 cycles. Subjects continued receiving treatment with trastuzumab SC for another 12 cycles (if SC treatment is well tolerated, otherwise subjects continued IV treatment) for a total of 18 cycles of treatment during the study.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered at a dose of 6 milligrams per kilogram (mg/kg) IV in 21-day cycles as per schedule described in respective arm.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Trastuzumab was administered at a dose of 600 milligrams per 5 milliliter (mg/5mL) SC in 21-day cycles as per schedule described in respective arm.

Number of subjects in period 1	Trastuzumab SC then IV	Trastuzumab IV then SC
Started	57	57
Completed	44	38
Not completed	13	19
Consent withdrawn by subject	4	4
Failure to return	1	-
Death	2	4
Unknown reason	-	3
Disease progression/recurrence of disease	3	3
Protocol deviation	1	5
Did not cooperate	2	-

Baseline characteristics

Reporting groups

Reporting group title	Trastuzumab SC then IV

Reporting group description:

Subjects received treatment with Trastuzumab IV for the first 3 cycles (cycle length = 21 days) followed by Trastuzumab SC for the next 3 cycles. Subjects continued receiving treatment with trastuzumab SC for another 12 cycles (if SC treatment is well tolerated, otherwise subjects continued IV treatment) for a total of 18 cycles of treatment during the study.

Reporting group title	Trastuzumab IV then SC

Reporting group description:

Subjects received treatment with Trastuzumab SC for the first 3 cycles (cycle length = 21 days) followed by Trastuzumab IV for the next 3 cycles. Subjects continued receiving treatment with trastuzumab SC for another 12 cycles (if SC treatment is well tolerated, otherwise subjects continued IV treatment) for a total of 18 cycles of treatment during the study.

Reporting group values	Trastuzumab SC then IV	Trastuzumab IV then SC	Total
Number of subjects	57	57	114
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)	40	41	81
From 65-84 years	17	16	33
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	58.23	59.15	
full range (min-max)	37.3 to 82.2	34.7 to 84.9	-
Gender Categorical Units: Subjects			
Female	57	57	114
Male	0	0	0

Subject analysis sets

Subject analysis set title	Trastuzumab SC Then Trastuzumab IV mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intent-to-Treat (m-ITT) population: all subjects from the ITT population who received both routes (SC and IV) during the cross-over period and who completed the last question of the PPQ after the cross-over period

Subject analysis set title	Trastuzumab IV Then Trastuzumab SC mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intent-to-Treat (m-ITT) population: all subjects from the ITT population who received both routes (SC and IV) during the cross-over period and who completed the last question of the PPQ after the cross-over period

Subject analysis set title	Trastuzumab SC Then Trastuzumab IV ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects who received at least one dose of T SC or T IV during the cross-over period

Subject analysis set title	Trastuzumab IV Then Trastuzumab SC ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects who received at least one dose of T SC or T IV during the cross-over period

Subject analysis set title	Trastuzumab SC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All randomized subjects who received at least one dose of Trastuzumab SC during the cross-over period.

Subject analysis set title	Trastuzumab IV
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All randomized subjects who received at least one dose of Trastuzumab IV during the cross-over period.

Reporting group values	Trastuzumab SC Then Trastuzumab IV mITT	Trastuzumab IV Then Trastuzumab SC mITT	Trastuzumab SC Then Trastuzumab IV ITT
Number of subjects	47	45	57
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)	33	32	40
From 65-84 years	12	15	17
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	58.24	57.36	58.23
full range (min-max)	39.9 to 84.1	37.3 to 80.5	37.3 to 82.2
Gender Categorical Units: Subjects			
Female	45	47	57
Male	0	0	0

Reporting group values	Trastuzumab IV Then Trastuzumab SC ITT	Trastuzumab SC	Trastuzumab IV
Number of subjects	56	108	111
Age Categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	40		
From 65-84 years	16		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean	59.15		
full range (min-max)	34.7 to 84.9		
Gender Categorical			
Units: Subjects			
Female	56	111	108
Male	0	0	0

End points

End points reporting groups

Reporting group title	Trastuzumab SC then IV

Reporting group description:

Subjects received treatment with Trastuzumab IV for the first 3 cycles (cycle length = 21 days) followed by Trastuzumab SC for the next 3 cycles. Subjects continued receiving treatment with trastuzumab SC for another 12 cycles (if SC treatment is well tolerated, otherwise subjects continued IV treatment) for a total of 18 cycles of treatment during the study.

Reporting group title	Trastuzumab IV then SC

Reporting group description:

Subjects received treatment with Trastuzumab SC for the first 3 cycles (cycle length = 21 days) followed by Trastuzumab IV for the next 3 cycles. Subjects continued receiving treatment with trastuzumab SC for another 12 cycles (if SC treatment is well tolerated, otherwise subjects continued IV treatment) for a total of 18 cycles of treatment during the study.

Subject analysis set title	Trastuzumab SC Then Trastuzumab IV mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intent-to-Treat (m-ITT) population: all subjects from the ITT population who received both routes (SC and IV) during the cross-over period and who completed the last question of the PPQ after the cross-over period

Subject analysis set title	Trastuzumab IV Then Trastuzumab SC mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified Intent-to-Treat (m-ITT) population: all subjects from the ITT population who received both routes (SC and IV) during the cross-over period and who completed the last question of the PPQ after the cross-over period

Subject analysis set title	Trastuzumab SC Then Trastuzumab IV ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects who received at least one dose of T SC or T IV during the cross-over period

Subject analysis set title	Trastuzumab IV Then Trastuzumab SC ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects who received at least one dose of T SC or T IV during the cross-over period

Subject analysis set title	Trastuzumab SC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All randomized subjects who received at least one dose of Trastuzumab SC during the cross-over period.

Subject analysis set title	Trastuzumab IV
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All randomized subjects who received at least one dose of Trastuzumab IV during the cross-over period.

Primary: Percentage of Subjects With Preference for Either IV or SC Route of Administration According to Subjects Preference Questionnaire (PPQ) Score

End point title	Percentage of Subjects With Preference for Either IV or SC Route of Administration According to Subjects Preference Questionnaire (PPQ) Score[1]

End point description:

The analysis of the primary preference endpoint is presented in the m-ITT population (and in the PP population for the sensitivity primary analysis).

End point type	Primary

End point timeframe:

Baseline up to 6 cycles (cycle length = 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 statistical analyses provided.

End point values	Trastuzumab SC Then Trastuzumab IV mITT	Trastuzumab IV Then Trastuzumab SC mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	45		
Units: Percentage				
number (not applicable)				
Subjects preference to intravenous injection	12.8	15.6		
Subjects preference to subcutaneous injection	87.2	84.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events

End point title	Percentage of Subjects With Adverse Events

End point description:

End point type	Secondary

End point timeframe:

Approximately 6 years

End point values	Trastuzumab SC	Trastuzumab IV		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	108	111		
Units: Number				
number (not applicable)	91.7	43.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Health Care Professionals With Preference for Either SC or IV Administration According to Health Care Professional Questionnaire (HCPQ) Score

End point title	Percentage of Health Care Professionals With Preference for Either SC or IV Administration According to Health Care Professional Questionnaire (HCPQ) Score

End point description:

Intent to treat: all randomized subjects who received at least one dose of T SC or T IV during the cross-over period

End point type	Secondary

End point timeframe:

Baseline up to 6 cycles (cycle length = 21 days)

End point values	Trastuzumab SC Then Trastuzumab IV ITT	Trastuzumab IV Then Trastuzumab SC ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52	47		
Units: Percentage				
number (not applicable)				
IV	13.5	10.6		
No preference	21.2	27.7		
SC	65.4	61.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 6 years	
Adverse event reporting additional description:	
Safety (SAF) population: all enrolled subjects who received at least one dose of study medication (T SC or T IV)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Trastuzumab SC
Reporting group description:	
All randomized subjects who received at least one dose of Trastuzumab SC during the cross-over period.	
Reporting group title	Long-term follow-up period
Reporting group description:	
After the 1-year T treatment period, subjects were switched to standard treatment, according to Investigator's choice and continued to be followed as recommended in routine clinical practice (every 6 months to assess vital status, disease progression and cardiac function) for additional 3 years.	
Reporting group title	Trastuzumab IV
Reporting group description:	
All randomized subjects who received at least one dose of Trastuzumab IV during the cross-over period.	

Serious adverse events	Trastuzumab SC	Long-term follow-up period	Trastuzumab IV
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 108 (12.04%)	4 / 113 (3.54%)	3 / 111 (2.70%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
LEUKAEMIA			
subjects affected / exposed	0 / 108 (0.00%)	1 / 113 (0.88%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Injury, poisoning and procedural complications			
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (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

ANKLE FRACTURE			
subjects affected / exposed	4 / 108 (3.70%)	0 / 113 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE			
subjects affected / exposed	0 / 108 (0.00%)	1 / 113 (0.88%)	0 / 111 (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
PROCEDURAL PAIN			
subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (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
WRONG PRODUCT ADMINISTERED			
subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (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
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 108 (0.00%)	0 / 113 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 108 (0.00%)	0 / 113 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPILEPSY			
subjects affected / exposed	0 / 108 (0.00%)	0 / 113 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
MUCOSAL INFLAMMATION			

subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (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
Gastrointestinal disorders			
ANAL FISSURE			
subjects affected / exposed	0 / 108 (0.00%)	1 / 113 (0.88%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
subjects affected / exposed	0 / 108 (0.00%)	0 / 113 (0.00%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
METRORRHAGIA			
subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (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
Respiratory, thoracic and mediastinal disorders			
LUNG DISORDER			
subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (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
RESPIRATORY DISTRESS			
subjects affected / exposed	0 / 108 (0.00%)	1 / 113 (0.88%)	0 / 111 (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
Hepatobiliary disorders			
CHOLELITHIASIS			
subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (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
CHOLESTASIS			

subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Renal and urinary disorders			
RENAL FAILURE			
subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (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
Infections and infestations			
ERYSIPELAS			
subjects affected / exposed	2 / 108 (1.85%)	0 / 113 (0.00%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (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
Product issues			
DEVICE DISLOCATION			
subjects affected / exposed	1 / 108 (0.93%)	0 / 113 (0.00%)	0 / 111 (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

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

Non-serious adverse events	Trastuzumab SC	Long-term follow-up period	Trastuzumab IV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 108 (91.67%)	17 / 113 (15.04%)	44 / 111 (39.64%)
Investigations			
WEIGHT INCREASED			
subjects affected / exposed	11 / 108 (10.19%)	0 / 113 (0.00%)	0 / 111 (0.00%)
occurrences (all)	11	0	0
EJECTION FRACTION DECREASED			
subjects affected / exposed	3 / 108 (2.78%)	2 / 113 (1.77%)	1 / 111 (0.90%)
occurrences (all)	4	3	1

WEIGHT DECREASED			
subjects affected / exposed	9 / 108 (8.33%)	0 / 113 (0.00%)	1 / 111 (0.90%)
occurrences (all)	9	0	1
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	6 / 108 (5.56%)	2 / 113 (1.77%)	3 / 111 (2.70%)
occurrences (all)	10	3	5
HAEMATOMA			
subjects affected / exposed	6 / 108 (5.56%)	0 / 113 (0.00%)	0 / 111 (0.00%)
occurrences (all)	8	0	0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	14 / 108 (12.96%)	3 / 113 (2.65%)	2 / 111 (1.80%)
occurrences (all)	30	3	4
PARAESTHESIA			
subjects affected / exposed	4 / 108 (3.70%)	1 / 113 (0.88%)	2 / 111 (1.80%)
occurrences (all)	6	1	2
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	31 / 108 (28.70%)	2 / 113 (1.77%)	4 / 111 (3.60%)
occurrences (all)	36	2	4
INJECTION SITE PAIN			
subjects affected / exposed	30 / 108 (27.78%)	0 / 113 (0.00%)	1 / 111 (0.90%)
occurrences (all)	53	0	1
INJECTION SITE ERYTHEMA			
subjects affected / exposed	17 / 108 (15.74%)	0 / 113 (0.00%)	0 / 111 (0.00%)
occurrences (all)	46	0	0
FATIGUE			
subjects affected / exposed	5 / 108 (4.63%)	0 / 113 (0.00%)	2 / 111 (1.80%)
occurrences (all)	7	0	2
PYREXIA			
subjects affected / exposed	4 / 108 (3.70%)	0 / 113 (0.00%)	2 / 111 (1.80%)
occurrences (all)	4	0	5
INJECTION SITE HAEMATOMA			
subjects affected / exposed	5 / 108 (4.63%)	0 / 113 (0.00%)	1 / 111 (0.90%)
occurrences (all)	5	0	1

Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	7 / 108 (6.48%)	1 / 113 (0.88%)	2 / 111 (1.80%)
occurrences (all)	7	1	2
NAUSEA			
subjects affected / exposed	7 / 108 (6.48%)	0 / 113 (0.00%)	2 / 111 (1.80%)
occurrences (all)	7	0	2
VOMITING			
subjects affected / exposed	5 / 108 (4.63%)	0 / 113 (0.00%)	1 / 111 (0.90%)
occurrences (all)	5	0	4
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	7 / 108 (6.48%)	1 / 113 (0.88%)	1 / 111 (0.90%)
occurrences (all)	8	1	1
COUGH			
subjects affected / exposed	4 / 108 (3.70%)	0 / 113 (0.00%)	2 / 111 (1.80%)
occurrences (all)	4	0	2
Skin and subcutaneous tissue disorders			
ERYTHEMA			
subjects affected / exposed	6 / 108 (5.56%)	0 / 113 (0.00%)	0 / 111 (0.00%)
occurrences (all)	7	0	0
PRURITUS			
subjects affected / exposed	6 / 108 (5.56%)	0 / 113 (0.00%)	0 / 111 (0.00%)
occurrences (all)	7	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	16 / 108 (14.81%)	0 / 113 (0.00%)	4 / 111 (3.60%)
occurrences (all)	17	0	5
MUSCLE SPASMS			
subjects affected / exposed	10 / 108 (9.26%)	0 / 113 (0.00%)	2 / 111 (1.80%)
occurrences (all)	11	0	2
BACK PAIN			
subjects affected / exposed	6 / 108 (5.56%)	1 / 113 (0.88%)	3 / 111 (2.70%)
occurrences (all)	6	1	3
PAIN IN EXTREMITY			

subjects affected / exposed	6 / 108 (5.56%)	0 / 113 (0.00%)	0 / 111 (0.00%)
occurrences (all)	7	0	0
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	13 / 108 (12.04%)	0 / 113 (0.00%)	3 / 111 (2.70%)
occurrences (all)	15	0	3
RHINITIS			
subjects affected / exposed	6 / 108 (5.56%)	1 / 113 (0.88%)	2 / 111 (1.80%)
occurrences (all)	6	1	2
NASOPHARYNGITIS			
subjects affected / exposed	5 / 108 (4.63%)	0 / 113 (0.00%)	2 / 111 (1.80%)
occurrences (all)	5	0	2
URINARY TRACT INFECTION			
subjects affected / exposed	4 / 108 (3.70%)	3 / 113 (2.65%)	0 / 111 (0.00%)
occurrences (all)	4	4	0
INFLUENZA			
subjects affected / exposed	6 / 108 (5.56%)	1 / 113 (0.88%)	1 / 111 (0.90%)
occurrences (all)	6	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2013	In order to match to clinical practice, the screening period was enlarged (between Day -21 to Day 1 instead of Day -14 to Day 1) In order to match to clinical practice, the 9th inclusion criterion (mBC) was simplified Due to the modification of the Herceptin SC SPC, the 11th inclusion criterion was changed, as well as the modalities of treatment use
21 June 2013	Times windows were added for the visits during the treatment period and the safety follow-up visit (±2 days) and for the long-term follow-up visits (±7 days) In order to match to clinical practice, the 9th inclusion criterion (mBC) was simplified
30 January 2014	In order to match to clinical practice, cardiac safety assessments were required every 6 cycles (instead of 3)
20 April 2015	Due to the extension of the inclusion period (from 1 to 2 years), the total study duration covered 6 years instead of 5 years. After the 1-year T treatment period, patients were followed up to 3 additional years even in the event of disease progression in the meantime, to allow overall survival estimation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28648618