



Clinical trial results:

A phase III clinical trial to evaluate patient's preference of subcutaneous trastuzumab (SC) versus intravenous (IV) administration in patients with HER2 positive Advanced Breast Cancer (ABC) who have received intravenous trastuzumab at least 4 months and without disease progression

Summary

EudraCT number	2012-004928-38
Trial protocol	ES
Global end of trial date	30 April 2018

Results information

Result version number	v1 (current)
This version publication date	29 October 2020
First version publication date	29 October 2020

Trial information

Trial identification

Sponsor protocol code	GEICAM/2012-07
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01875367
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GEICAM (FUNDACIÓN GRUPO ESPAÑOL DE INVESTIGACIÓN EN CÁNCER DE MAMA)
Sponsor organisation address	Avenida de los Pirineos 7, San Sebastián de los Reyes / Madrid, Spain, 28703
Public contact	GEICAM, GEICAM (Fundación Grupo Español de Investigación en Cáncer de Mama), 0034 916592870, inicio_ensayos@geicam.org
Scientific contact	GEICAM, GEICAM (Fundación Grupo Español de Investigación en Cáncer de Mama), 0034 916592870, inicio_ensayos@geicam.org

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	30 April 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To analyze the percentage of patients who indicate a preference for the use of the subcutaneous vs the intravenous administration of trastuzumab.

Protection of trial subjects:

Not applicable. It was not necessary to applied extra measures for protection of the subjects out of the good clinical practice environment.

Background therapy:

HER2 receptor is involved in cell growth control, differentiation, and survival (Gschwind, Fischer, & Ullrich, 2004; Yarden & Sliwkowski, 2001). HER2 oncogen, overexpressed in 20%-30% of breast cancer (BC) patients, is associated with aggressive tumor characteristics and poor prognosis (Slamon et al., 1987; Slamon et al., 1989). (Menard, Fortis, Castiglioni, Agresti, & Balsari, 2001; Ross & Fletcher, 1998). Trastuzumab, a humanized anti-HER2 monoclonal antibody, is the standard of care in monotherapy or in combination. As far as 1-year of treatment in the early disease setting and maintenance therapy in patients with metastatic breast cancer (MBC) is recommended, HER2-positive BC patients undergo long periods on trastuzumab therapy. Standard trastuzumab is administered intravenously (IV-t) according to weight every 3 weeks. IV-t initial administration lasts 90min and subsequent 30min, resulting in infusion reactions, venous access problems, long administration and observation periods, frequent visits to hospital, and the need for reloading dosages in case of treatment delays.

Evidence for comparator:

The subcutaneous formulation of trastuzumab (SC-t) was developed as an alternative to the IV formulation and it is administered as a 600mg-fixed dose, combined with 10,000U of recombinant human hyaluronidase (rHuPH20), in a single injection (vial) or in a single injection device (SID) in 5-minutes. SC-t shortens administration time and errors by eliminating weightbased dose loading. Whereas HannaH, PrefHER and SafeHER studies showed that pharmacokinetics, efficacy and safety of SC-t was comparable to IV-t in early HER2-positive BC (Gligorov et al., 2017; Ismael et al., 2012; Pivot et al., 2017), data for MBC patients are lacking. Our aim was to evaluate HER2-positive MBC patients' preference for IV-t versus SC-t.

Actual start date of recruitment	18 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 166
Worldwide total number of subjects	166
EEA total number of subjects	166

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)	105
From 65 to 84 years	57
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

From September 2013 to July 2015, 166 patients were randomized (81 to arm A [vial to SID] and 85 to arm B [SID to vial]) in 26 GEICAM Spanish Breast Cancer Group sites.

Pre-assignment

Screening details:

From September 2013 to July 2015, 166 patients were randomized (81 to arm A [vial to SID] and 85 to arm B [SID to vial]) in 26 GEICAM Spanish Breast Cancer Group sites.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	T-SC Vial + T-SC Device

Arm description:

Trastuzumab Injectable Solution: Subcutaneous (SC) injection vial with a fixed dose of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) identical to that provided by the device. 3 weeks x 2 cycles

Trastuzumab Injectable Solution: Subcutaneous injection vial with a fixed dose of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) identical to that provided by the device. 3 weeks x 2 cycles.

Trastuzumab Injectable Product: Single injection device is provided and loaded with the mixture of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) and is ready for use. 3 weeks x 2 cycles

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

Dosage and administration details:

Subcutaneous injection vial with a fixed dose of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) identical to that provided by the device. 3 weeks x 2 cycles.

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

Dosage and administration details:

Single injection device is provided and loaded with the mixture of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) and is ready for use. 3 weeks x 2 cycles

Arm title	T-SC Device + T-SC Vial
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Arm description:

Trastuzumab Injectable Product: Single injection device is provided and loaded with the mixture of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) and is ready for use. 3 weeks x 2 cycles

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

Dosage and administration details:

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Number of subjects in period 1	T-SC Vial + T-SC Device	T-SC Device + T-SC Vial
Started	81	85
Completed	76	83
Not completed	5	2
Not receive study treatment	1	-
Not complete at least 2 questionnaires	4	2

Baseline characteristics

Reporting groups

Reporting group title	T-SC Vial + T-SC Device
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Reporting group description:

Trastuzumab Injectable Solution: Subcutaneous (SC) injection vial with a fixed dose of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) identical to that provided by the device. 3 weeks x 2 cycles

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Reporting group title	T-SC Device + T-SC Vial
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Reporting group description:

Trastuzumab Injectable Product: Single injection device is provided and loaded with the mixture of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) and is ready for use. 3 weeks x 2 cycles

Trastuzumab Injectable Solution: Subcutaneous injection vial with a fixed dose of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) identical to that provided by the device. 3 weeks x 2 cycles.

Trastuzumab Injectable Product: Single injection device is provided and loaded with the mixture of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) and is ready for use. 3 weeks x 2 cycles

Reporting group values	T-SC Vial + T-SC Device	T-SC Device + T-SC Vial	Total
Number of subjects	81	85	166
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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	63	58	
full range (min-max)	35 to 93	38 to 85	-
Gender categorical Units: Subjects			
Female	81	85	166
Male	0	0	0
Race Units: Subjects			
Caucasian	78	83	161
Black	1	0	1
Hispanic	1	0	1

Arabian	1	2	3
Menopausal status			
Units: Subjects			
Premenopausal	8	12	20
Postmenopausal	73	73	146
Eastern Cooperative Oncology Group (ECOG) performance status			
Measure Description: ECOG score runs from 0 to 5, with 0 denoting perfect health and 5 death. 0 - Asymptomatic 1 - Symptomatic but completely ambulatory 2 - Symptomatic, <50% in bed during the day 3 - Symptomatic, >50% in bed, but not bedbound 4 - Bedbound 5 - Death			
Units: Subjects			
ECOG 0	63	61	124
ECOG 1	17	24	41
ECOG 2	1	0	1
Estrogen Receptor			
A cancer is called hormonal receptor positive if it has receptors for progesterone or estrogen. This suggests that the cancer cells, like normal breast cells, may receive signals from progesterone or estrogen that could promote their growth. If the cancer is hormone-receptor-negative (no receptors are present), then hormonal therapy is unlikely to work.			
Units: Subjects			
Positive	46	60	106
Negative	35	25	60
Progesterone Receptor			
A cancer is called hormonal receptor positive if it has receptors for progesterone or estrogen. This suggests that the cancer cells, like normal breast cells, may receive signals from progesterone or estrogen that could promote their growth. If the cancer is hormone-receptor-negative (no receptors are present), then hormonal therapy is unlikely to work.			
Units: Subjects			
Negative	50	38	88
Positive	31	47	78
Other anti HER2 therapy at registration			
Units: Subjects			
Pertuzumab	8	11	19
Lapatinib	3	5	8
No anti HER2 therapy	70	69	139
Treatment combined with trastuzumab at registration			
Units: Subjects			
Hormonotherapy	34	36	70
Chemotherapy	12	9	21
Other anticancertherapy	7	10	17
Other anticancer therapy plus Chemotherapyplus	2	4	6
Other anticancer therapy plus Hormonotherapy plus	2	2	4
No other anticancer therapy	24	24	48
Administration route at registration			
Units: Subjects			
Intravenous	25	27	52
Intramuscular	5	5	10

Subcutaneous	4	5	9
Oral	25	29	54
None	22	19	41
Metastases at diagnosis Units: Subjects			
No	53	52	105
Yes	28	33	61
Visceral metastases at registration Units: Subjects			
Yes	41	49	90
No	40	36	76
Bone metastases at registration Units: Subjects			
Yes	34	41	75
No	47	44	91
Skin/soft tissue/lymph nodes metastases at registration Units: Subjects			
Yes	31	29	60
No	50	56	106
Time with IV trastuzumab for metastasis at registration Units: Years			
median	1.9	1.78	
full range (min-max)	0.35 to 13.67	0.34 to 14.05	-
Prior treatment lines at registration Units: Treatment lines			
median	1	1	
full range (min-max)	1 to 7	1 to 7	-

End points

End points reporting groups

Reporting group title	T-SC Vial + T-SC Device
Reporting group description:	
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Reporting group title	T-SC Device + T-SC Vial
Reporting group description:	
Trastuzumab Injectable Product: Single injection device is provided and loaded with the mixture of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) and is ready for use. 3 weeks x 2 cycles	
Trastuzumab Injectable Solution: Subcutaneous injection vial with a fixed dose of trastuzumab (600mg) and recombinant human hyaluronidase (10.000U) identical to that provided by the device. 3 weeks x 2 cycles.	
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Primary: Percentage of Treatment Preference

End point title	Percentage of Treatment Preference
End point description:	
The percentage of patients who indicate a preference for the use of the intravenous vs subcutaneous administration of trastuzumab was analyzed with the answer to the questionnaire C2 (question number 39) of experiences and preferences of the patient.	
End point type	Primary
End point timeframe:	
Up to 12 weeks	

End point values	T-SC Vial + T-SC Device	T-SC Device + T-SC Vial		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	83		
Units: Preference				
Subcutaneous	66	71		
Intravenous	6	5		
No preference	4	7		

Statistical analyses

Statistical analysis title	Proportion estimation
Statistical analysis description: Percent preference of SC in both arms was calculated and 95% confidential interval and it was compared with the 75% prefixed.	
Comparison groups	T-SC Vial + T-SC Device v T-SC Device + T-SC Vial
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0008
Method	Chi-squared
Parameter estimate	percentage
Point estimate	86.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	79.8
upper limit	91.1
Variability estimate	Standard deviation

Secondary: Percentage of Subcutaneous Treatment (Vial vs Device Administration) Preference

End point title	Percentage of Subcutaneous Treatment (Vial vs Device Administration) Preference
End point description: The percentage of patients who indicate a preference for the use of SC administration by road or device was analyzed. This was discussed in the answer to question number 28 of the questionnaire of experiences and preferences of the patient.	
End point type	Secondary
End point timeframe: Up to 12 weeks	

End point values	T-SC Vial + T-SC Device	T-SC Device + T-SC Vial		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	77		
Units: Patients				
Subcutaneous	46	44		
Intravenous	20	20		
No preference	4	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Medical Staff Satisfaction Intravenous vs Subcutaneous

End point title	Medical Staff Satisfaction Intravenous vs Subcutaneous ^[1]
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End point description:

The medical staff satisfaction was analyzed with the answers to question number 33a of the questionnaire of experiences and preferences of the medical staff.

End point type	Secondary
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End point timeframe:

Up to 12 weeks

Notes:

[1] - 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: The medical staff satisfaction has been analysed taken into account only the device type, and not the arm. It is the preference of health staff and is a different sample from both arms.

End point values	T-SC Vial + T-SC Device			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Answers from questionnaire				
Subcutaneous	34			
Intravenous	0			
No differences	4			
Not answered	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Medical Staff Satisfaction Subcutaneous Device vs Vial

End point title	Medical Staff Satisfaction Subcutaneous Device vs Vial ^[2]
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End point description:

The medical staff satisfaction was analyzed with the answers to question number 33b of the questionnaire of experiences and preferences of the medical staff.

End point type	Secondary
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End point timeframe:

Up to 12 weeks

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: The medical staff satisfaction has been analysed taken into account only the device type, and not the arm. It is the preference of health staff and is a different sample from both arms.

End point values	T-SC Device + T-SC Vial			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Answers from questionnaire				
Preferred device	20			
Preferred vial	11			

No Preference	8			
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Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants Who Experienced Adverse Events (AE)

End point title	The Number of Participants Who Experienced Adverse Events (AE)
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End point description:

Safety was assessed by standard clinical and laboratory tests (haematology, serum chemistry). AE grade were defined by the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 4.03.

End point type	Secondary
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End point timeframe:

Through study treatment, an average of 16 weeks

End point values	T-SC Vial + T-SC Device	T-SC Device + T-SC Vial		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	85		
Units: Events				
The Number of Participants Who Experienced Adverse	76	84		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were reported after Informed Consent Document (ICD) and before study drugs until approximately 30 days following the discontinuation of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	T-SC Vial + T-SC Device
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Reporting group description: -

Reporting group title	T-SC Device + T-SC Vial
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Reporting group description: -

Serious adverse events	T-SC Vial + T-SC Device	T-SC Device + T-SC Vial	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 81 (2.47%)	10 / 85 (11.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Heart Failure			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
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			

Fever			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Nodule in left breast			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodule in right breast			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgery for surgical castration			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lack of strength in left leg			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ostenecrosis produced by biphosphonates			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cold			

subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection (Bacteriemia)			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	T-SC Vial + T-SC Device	T-SC Device + T-SC Vial	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 81 (93.83%)	84 / 85 (98.82%)	
Investigations			
Platelet count decreased grade 4			
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased grade 1			
subjects affected / exposed	4 / 81 (4.94%)	8 / 85 (9.41%)	
occurrences (all)	4	8	
Creatinine increased grade 4			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Creatinine increased grade 2			
subjects affected / exposed	1 / 81 (1.23%)	2 / 85 (2.35%)	
occurrences (all)	1	2	
Creatinine increased grade 1			
subjects affected / exposed	13 / 81 (16.05%)	17 / 85 (20.00%)	
occurrences (all)	13	17	
Alanine aminotransferase increased grade 3			
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)	
occurrences (all)	0	1	
Alanine aminotransferase increased grade 2			

subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Alanine aminotransferase increased grade 1		
subjects affected / exposed	16 / 81 (19.75%)	10 / 85 (11.76%)
occurrences (all)	16	10
Aspartate aminotransferase increased grade 3		
subjects affected / exposed	0 / 81 (0.00%)	1 / 85 (1.18%)
occurrences (all)	0	1
Aspartate aminotransferase increased grade 1		
subjects affected / exposed	15 / 81 (18.52%)	17 / 85 (20.00%)
occurrences (all)	15	17
Alkaline phosphatase increased grade 3		
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)
occurrences (all)	1	0
Alkaline phosphatase increased grade 2		
subjects affected / exposed	1 / 81 (1.23%)	2 / 85 (2.35%)
occurrences (all)	1	2
Alkaline phosphatase increased grade 1		
subjects affected / exposed	12 / 81 (14.81%)	15 / 85 (17.65%)
occurrences (all)	12	15
Diarrhea grade 2		
subjects affected / exposed	0 / 81 (0.00%)	4 / 85 (4.71%)
occurrences (all)	0	4
Hemoglobin increased grade 3		
subjects affected / exposed	1 / 81 (1.23%)	0 / 85 (0.00%)
occurrences (all)	1	0
Neutrophil count decreased grade 3		
subjects affected / exposed	2 / 81 (2.47%)	0 / 85 (0.00%)
occurrences (all)	2	0
Neutrophil count decreased grade 2		
subjects affected / exposed	7 / 81 (8.64%)	5 / 85 (5.88%)
occurrences (all)	7	5
Neutrophil count decreased grade 1		

subjects affected / exposed occurrences (all)	13 / 81 (16.05%) 13	13 / 85 (15.29%) 13	
White blood cells decreased grade 2 subjects affected / exposed occurrences (all)	7 / 81 (8.64%) 7	5 / 85 (5.88%) 5	
White blood cells decreased grade 1 subjects affected / exposed occurrences (all)	15 / 81 (18.52%) 15	17 / 85 (20.00%) 17	
Cardiac disorders Heart failure grade 3 subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 85 (1.18%) 1	
General disorders and administration site conditions Fatigue grade 3 subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 85 (1.18%) 1	
Fatigue grade 2 subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 3	5 / 85 (5.88%) 5	
Fatigue grade 1 subjects affected / exposed occurrences (all)	10 / 81 (12.35%) 10	16 / 85 (18.82%) 16	
Injection site reaction grade 2 subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	3 / 85 (3.53%) 3	
Injection site reaction grade 1 subjects affected / exposed occurrences (all)	9 / 81 (11.11%) 9	6 / 85 (7.06%) 6	
Blood and lymphatic system disorders Anemia grade 2 subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5	2 / 85 (2.35%) 2	
Anemia grade 1 subjects affected / exposed occurrences (all)	27 / 81 (33.33%) 27	32 / 85 (37.65%) 32	
Reproductive system and breast disorders			

Nodule in left breast grade 3 subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 85 (1.18%) 1	
Gastrointestinal disorders			
Diarrhea grade 3 subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 85 (0.00%) 0	
Diarrhea grade 1 subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 6	5 / 85 (5.88%) 5	
Nausea grade 3 subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 85 (0.00%) 0	
Nausea grade 2 subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 85 (0.00%) 0	
Nausea grade 1 subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 4	0 / 85 (0.00%) 0	
Vomiting grade 3 subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 85 (0.00%) 0	
Vomiting grade 2 subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	0 / 85 (0.00%) 0	
Vomiting grade 1 subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 85 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Voice alteration grade 3 subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 85 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis of jaw grade 3 subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 85 (1.18%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2013	The modification of the moment of blood draw of the first blood sample for participation in the optional immunogenicity study: As indicated in the protocol version 1 of October 19, 2012, this sample should be obtained within 14 days prior to the inclusion of the patient in the study. It is considered necessary to postpone this blood draw and perform it before the administration of the first cycle of subcutaneous trastuzumab, as it seems more appropriate than the blood draw of a sample for participation in an optional study is carried out once the patient has been included in the study, after all screening tests have been performed and all the selection criteria have been met. This also ensures that the sample is obtained at the same time for all patients. Errata correction and typographical errors.
14 February 2014	Immunogenicity sub-study has been eliminated due to it is not possible to carry out. To allow other immunotherapy, including humanized anti-HER2 antibodies, so it is possible to include patients under pertuzumab treatment (approved in combination with trastuzumab for first line). To change the obtaining date of the first questionnaire about the patient's experiences and preferences (C1), to be required after the randomization and before the administration of the first subcutaneous trastuzumab cycle (instead of within 14 days prior to the inclusion), because it is more appropriate for the patient to complete this specific study procedure once it has been included in the study. HER2 positive criteria have been updated according to the 2013 ASCO / CAP guidelines. Trastuzumab investigator brochure has been updated to version 14 of October 2013 To incorporate 19 sites in the study. Also typographical errors were corrected.
31 March 2016	The trastuzumab single-use injection device is no longer to be supplied in the study, because laboratory has decided to cease its manufacturing. The decision to discontinue SID manufacturing was not due to any SID safety or quality concerns. The device is one of the two subcutaneous (SC) formulations provided in this study and this fact does not impact in the supply of the other formulation, the SC trastuzumab with vial. This amendment includes also the sample size decrease (from 195 to 160 patients) based on the updated and published results on the preference rate of other study with SC vs IV trastuzumab (PrefHER). Administrative changes and grammatical mistakes were corrected

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

We do not have longterm follow-up data of the SC-t efficacy.
Device SC-t SID has not been commercialized.
All patients had already been treated with IV-t for at least 4 months without disease progression prior to the study entry.

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32578279>