# 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 |

**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 inyection 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 |

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
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 inyection 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

| **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 questionaries | 4 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | T-SC Vial + T-SC Device |
| 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<br>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.<br>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 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<br>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.<br>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<br>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<br>Units: years | | | |
| median | 63 | 58 | |
| full range (min-max) | 35 to 93 | 38 to 85 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 81 | 85 | 166 |
| Male | 0 | 0 | 0 |
| Race<br>Units: Subjects | | | |
| Caucasian | 78 | 83 | 161 |
| Black | 1 | 0 | 1 |
| Hispanic | 1 | 0 | 1 |

| | | | |
|---|---|---|---|
| Arabian | 1 | 2 | 3 |
| Menopausal status<br>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.<br>0 - Asymptomatic<br>1 - Symptomatic but completely ambulatory<br>2 - Symptomatic, <50% in bed during the day<br>3 - Symptomatic, >50% in bed, but not bedbound<br>4 - Bedbound<br>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.<br>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.<br>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<br>Units: Subjects | | | |
| Pertuzumab | 8 | 11 | 19 |
| Lapatinib | 3 | 5 | 8 |
| No anti HER2 therapy | 70 | 69 | 139 |
| Treatment combined with trastuzumab at registration<br>Units: Subjects | | | |
| Hormonotherapy | 34 | 36 | 70 |
| Chamotherapy | 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<br>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<br>Units: Subjects | | | |
| No | 53 | 52 | 105 |
| Yes | 28 | 33 | 61 |
| Visceral metastases at registration<br>Units: Subjects | | | |
| Yes | 41 | 49 | 90 |
| No | 40 | 36 | 76 |
| Bone metastases at registration<br>Units: Subjects | | | |
| Yes | 34 | 41 | 75 |
| No | 47 | 44 | 91 |
| Skin/soft tissue/lymph nodes metastases at registration<br>Units: Subjects | | | |
| Yes | 31 | 29 | 60 |
| No | 50 | 56 | 106 |
| Time with IV trastuzumab for metastasis at registration<br>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<br>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: | |
| 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<br>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.<br>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 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<br>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.<br>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 | |

### 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] |
|---|---|

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 |
|---|---|

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 no 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] |
|---|---|

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 |
|---|---|

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 no 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 | | | |

## 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) |
|---|---|

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 |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | NCI-CTCAE |
| Dictionary version | 4.03 |

### Reporting groups

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

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

| | | | |
|---|---|---|---|
| Nodule in left breast grade 3 | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 85 (1.18%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Diarrhea grade 3 | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 85 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diarrhea grade 1 | | | |
| subjects affected / exposed | 6 / 81 (7.41%) | 5 / 85 (5.88%) | |
| occurrences (all) | 6 | 5 | |
| Nausea grade 3 | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 85 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nausea grade 2 | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 85 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nausea grade 1 | | | |
| subjects affected / exposed | 4 / 81 (4.94%) | 0 / 85 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Vomiting grade 3 | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 85 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vomiting grade 2 | | | |
| subjects affected / exposed | 2 / 81 (2.47%) | 0 / 85 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vomiting grade 1 | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 85 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Voice alteration grade 3 | | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 85 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteonecrosis of jaw grade 3 | | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 85 (1.18%) | |
| occurrences (all) | 0 | 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.<br>Errata correction and typographical errors. |
| 14 February 2014 | Immunogenicity sub-study has been eliminated due to it is not possible to carry out.<br>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).<br>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.<br>HER2 positive criteria have been updated according to the 2013 ASCO / CAP guidelines.<br>Trastuzumab investigator brochure has been updated to version 14 of October 2013 To incorporate 19 sites in the study.<br>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.<br>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).<br>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