



## Clinical trial results:

### HOMERUS: A Local, Open Label, Multicentre, Phase IIIB Study, Investigating Subcutaneous Trastuzumab Administered at Home With Single Injection Device in Patients With HER2-Positive Early Breast Cancer

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2013-000829-31    |
| Trial protocol           | NL                |
| Global end of trial date | 14 September 2018 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2               |
| This version publication date  | 18 December 2019 |
| First version publication date | 04 October 2019  |
| Version creation reason        |                  |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | ML28878 |
|-----------------------|---------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                                                             |
|------------------------------|-------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | F. Hoffmann-La Roche                                                                                        |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH4070                                                           |
| Public contact               | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +4161 6878333, global.trial_information@roche.com |
| Scientific contact           | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +4161 6878333, 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                       | 14 September 2018 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 14 September 2018 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

A study to investigate subcutaneous trastuzumab administration at home with a Single Injection Device in subjects with HER2-positive early breast cancer.

Protection of trial subjects:

Each subject or legally authorized representative signed an Informed Consent Form (ICF) before participating in this study.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 14 February 2014 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety           |
| Long term follow-up duration                              | 24 Months        |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Netherlands: 125 |
| Worldwide total number of subjects   | 125              |
| EEA total number of subjects         | 125              |

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)                      | 115 |
| From 65 to 84 years                       | 10  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Adult subjects With HER2-Positive Early Breast Cancer were included in this study.

### Period 1

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

### Arms

|           |             |
|-----------|-------------|
| Arm title | Trastuzumab |
|-----------|-------------|

Arm description:

Participants will receive 600 milligrams (mg) trastuzumab SC by single-use injection device (SID) every 3 weeks (Q3W) for up to a total of 1 year, unless disease recurrence, unacceptable toxicity or participant withdrawal occurs. The first 3 administrations will be done at hospital, after that participants will be permitted to self-administer under the supervision of a healthcare professional (HCP).

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

Dosage and administration details:

Participants received 600 milligrams (mg) trastuzumab subcutaneously (SC) by a single-use injection device (SID) every 3 weeks (Q3W) for up to a total of 1 year, unless disease recurrence, unacceptable toxicity or participant withdrawal occurred. The first 3 administrations were done at hospital, after that participants were permitted to self administer under the supervision of a healthcare professional (HCP).

| Number of subjects in period 1      | Trastuzumab |
|-------------------------------------|-------------|
| Started                             | 125         |
| Completed                           | 108         |
| Not completed                       | 17          |
| Consent withdrawn by subject        | 2           |
| Recurrence of disease               | 1           |
| Adverse event, non-fatal            | 9           |
| Administrative/other                | 1           |
| Violation of selection criteria     | 2           |
| Refused treatment/did not cooperate | 2           |



## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Trastuzumab |
|-----------------------|-------------|

Reporting group description:

Participants will receive 600 milligrams (mg) trastuzumab SC by single-use injection device (SID) every 3 weeks (Q3W) for up to a total of 1 year, unless disease recurrence, unacceptable toxicity or participant withdrawal occurs. The first 3 administrations will be done at hospital, after that participants will be permitted to self-administer under the supervision of a healthcare professional (HCP).

| Reporting group values                                | Trastuzumab | Total |  |
|-------------------------------------------------------|-------------|-------|--|
| Number of subjects                                    | 125         | 125   |  |
| Age categorical                                       |             |       |  |
| Units: Subjects                                       |             |       |  |
| In utero                                              | 0           | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0           | 0     |  |
| Newborns (0-27 days)                                  | 0           | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0           | 0     |  |
| Children (2-11 years)                                 | 0           | 0     |  |
| Adolescents (12-17 years)                             | 0           | 0     |  |
| Adults (18-64 years)                                  | 115         | 115   |  |
| From 65-84 years                                      | 10          | 10    |  |
| 85 years and over                                     | 0           | 0     |  |
| Age continuous                                        |             |       |  |
| Units: years                                          |             |       |  |
| arithmetic mean                                       | 50.7        |       |  |
| standard deviation                                    | ± 9.91      | -     |  |
| Gender categorical                                    |             |       |  |
| Units: Subjects                                       |             |       |  |
| Female                                                | 124         | 124   |  |
| Male                                                  | 1           | 1     |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                    |             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                              | Trastuzumab |
| Reporting group description:<br>Participants will receive 600 milligrams (mg) trastuzumab SC by single-use injection device (SID) every 3 weeks (Q3W) for up to a total of 1 year, unless disease recurrence, unacceptable toxicity or participant withdrawal occurs. The first 3 administrations will be done at hospital, after that participants will be permitted to self-administer under the supervision of a healthcare professional (HCP). |             |

### Primary: Percentage of Participants With Adverse Events (AEs) and Serious AEs (SAEs)

|                 |                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Adverse Events (AEs) and Serious AEs (SAEs) <sup>[1]</sup> |
|-----------------|--------------------------------------------------------------------------------------------|

End point description:

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline up to approximately 4 years

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 for this endpoint

| End point values              | Trastuzumab     |  |  |  |
|-------------------------------|-----------------|--|--|--|
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 125             |  |  |  |
| Units: percentage of subjects |                 |  |  |  |
| number (not applicable)       |                 |  |  |  |
| Treatment-Emergent AEs        | 96.8            |  |  |  |
| Treatment-Emergent SAEs       | 8.0             |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics Trough Concentrations (C<sub>trough</sub>) of Trastuzumab

|                 |                                                                              |
|-----------------|------------------------------------------------------------------------------|
| End point title | Pharmacokinetics Trough Concentrations (C <sub>trough</sub> ) of Trastuzumab |
|-----------------|------------------------------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose (within 1 day before trastuzumab administration) at Cycles 2, 3, 9, 10, 12, 13 (cycle length=21 days)

|                                      |                  |  |  |  |
|--------------------------------------|------------------|--|--|--|
| <b>End point values</b>              | Trastuzumab      |  |  |  |
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 0 <sup>[2]</sup> |  |  |  |
| Units: ug/mL                         |                  |  |  |  |
| arithmetic mean (standard deviation) | ()               |  |  |  |

Notes:

[2] - Data has not been analysed for reporting purposes

### Statistical analyses

No statistical analyses for this end point

### Secondary: Health Survey Short Form-36 (SF-36) Score

|                        |                                                                                 |
|------------------------|---------------------------------------------------------------------------------|
| End point title        | Health Survey Short Form-36 (SF-36) Score                                       |
| End point description: | SF-36 to assess Physical component score (PCS) and mental component score (MCS) |
| End point type         | Secondary                                                                       |
| End point timeframe:   | Cycles 3 and 9 (cycle length=21 days)                                           |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Trastuzumab     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 125             |  |  |  |
| Units: Score on a scale              |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| SF-36 PCS, Cycle 3 (n=109)           | 59.4 (± 18.90)  |  |  |  |
| SF-36 PCS, Cycle 9 (n=98)            | +6.9 (± 19.38)  |  |  |  |
| SF-36 MCS, Cycle 3 (n=106)           | 71.5 (± 18.88)  |  |  |  |
| SF-36 MCS, Cycle 9 (n=95)            | -0.3 (± 17.37)  |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mood and Anxiety Questionnaire (MASQ) Score

|                        |                                             |
|------------------------|---------------------------------------------|
| End point title        | Mood and Anxiety Questionnaire (MASQ) Score |
| End point description: |                                             |
| End point type         | Secondary                                   |
| End point timeframe:   | Cycles 3 and 9 (cycle length=21 days)       |

|                                              |                 |  |  |  |
|----------------------------------------------|-----------------|--|--|--|
| <b>End point values</b>                      | Trastuzumab     |  |  |  |
| Subject group type                           | Reporting group |  |  |  |
| Number of subjects analysed                  | 100             |  |  |  |
| Units: Scores on a scale                     |                 |  |  |  |
| arithmetic mean (standard deviation)         |                 |  |  |  |
| Anhedonic Depression, Cycle 9 (n=100)        | +0.2 (± 9.30)   |  |  |  |
| Anxious Arousal, Cycle 9 (n=100)             | +1.1 (± 7.83)   |  |  |  |
| General Distress Depression, Cycle 9 (n=100) | -0.1 (± 7.12)   |  |  |  |
| General Distress Anxiety, Cycle 9 (n=100)    | +0.4 (± 5.68)   |  |  |  |
| General Distress Mixed, Cycle 9 (n=100)      | -0.0 (± 6.00)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Choosing to Return to Hospital Administration

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Percentage of Subjects Choosing to Return to Hospital Administration |
|-----------------|----------------------------------------------------------------------|

End point description:

According to protocol, patients should have been given the choice to return to in-hospital administration at cycle 6, however the patients deciding to do so made that decision later on during the study. Due to ethical considerations (patient well-fare), this could not be refused. Analysing according to original endpoint would not reflect the actual course of the decision of patients to return to hospital administration. Therefore it was decided to analyse at later timepoints, deviating from the original endpoint.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 7 to Cycle 18 (cycle length=21 days)

|                               |                 |  |  |  |
|-------------------------------|-----------------|--|--|--|
| <b>End point values</b>       | Trastuzumab     |  |  |  |
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 114             |  |  |  |
| Units: Percentage of subjects |                 |  |  |  |
| number (not applicable)       |                 |  |  |  |
| Cycle 7 (n=114)               | 3.5             |  |  |  |
| Cycle 8 (n=114)               | 0.0             |  |  |  |
| Cycle 9 (n=112)               | 2.7             |  |  |  |
| Cycle 10 (n=112)              | 1.8             |  |  |  |
| Cycle 11 (n=109)              | 0.0             |  |  |  |
| Cycle 12 (n=108)              | 1.9             |  |  |  |
| Cycle 13 (n=100)              | 3.0             |  |  |  |
| Cycle 14 (n=99)               | 0.0             |  |  |  |

|                |     |  |  |  |
|----------------|-----|--|--|--|
| Cycle 15 (n=6) | 0.0 |  |  |  |
| Cycle 16 (n=6) | 0.0 |  |  |  |
| Cycle 17 (n=6) | 0.0 |  |  |  |
| Cycle 18 (n=6) | 0.0 |  |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline up to approximately 4 years

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Trastuzumab |
|-----------------------|-------------|

Reporting group description:

Participants will receive 600 milligrams (mg) trastuzumab SC by SID every 3 weeks (Q3W) for up to a total of 1 year, unless disease recurrence, unacceptable toxicity or participant withdrawal occurs. The first 3 administrations will be done at hospital, after that participants will be permitted to self-administer under the supervision of a healthcare professional (HCP).

| Serious adverse events                               | Trastuzumab      |  |  |
|------------------------------------------------------|------------------|--|--|
| Total subjects affected by serious adverse events    |                  |  |  |
| subjects affected / exposed                          | 10 / 125 (8.00%) |  |  |
| number of deaths (all causes)                        | 2                |  |  |
| number of deaths resulting from adverse events       | 0                |  |  |
| Injury, poisoning and procedural complications       |                  |  |  |
| Wound necrosis                                       |                  |  |  |
| subjects affected / exposed                          | 1 / 125 (0.80%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Cardiac disorders                                    |                  |  |  |
| Myocardial infarction                                |                  |  |  |
| subjects affected / exposed                          | 1 / 125 (0.80%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| General disorders and administration site conditions |                  |  |  |
| Influenza like illness                               |                  |  |  |
| subjects affected / exposed                          | 1 / 125 (0.80%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1            |  |  |
| deaths causally related to treatment / all           | 0 / 0            |  |  |
| Reproductive system and breast disorders             |                  |  |  |

|                                                 |                 |  |  |
|-------------------------------------------------|-----------------|--|--|
| Rectocele                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 125 (0.80%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Cholelithiasis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 125 (0.80%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Device related infection                        |                 |  |  |
| subjects affected / exposed                     | 1 / 125 (0.80%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sinusitis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 125 (0.80%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 125 (0.80%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mastitis                                        |                 |  |  |
| subjects affected / exposed                     | 2 / 125 (1.60%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

|                                                       |                    |  |  |
|-------------------------------------------------------|--------------------|--|--|
| <b>Non-serious adverse events</b>                     | Trastuzumab        |  |  |
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 119 / 125 (95.20%) |  |  |
| Vascular disorders                                    |                    |  |  |
| Hot flush                                             |                    |  |  |

|                                                      |                                 |  |  |
|------------------------------------------------------|---------------------------------|--|--|
| subjects affected / exposed                          | 40 / 125 (32.00%)               |  |  |
| occurrences (all)                                    | 41                              |  |  |
| Hypertension                                         |                                 |  |  |
| subjects affected / exposed                          | 26 / 125 (20.80%)               |  |  |
| occurrences (all)                                    | 32                              |  |  |
| General disorders and administration site conditions |                                 |  |  |
| Chest pain                                           |                                 |  |  |
| subjects affected / exposed                          | 8 / 125 (6.40%)                 |  |  |
| occurrences (all)                                    | 8                               |  |  |
| Influenza type illness                               |                                 |  |  |
| subjects affected / exposed                          | 18 / 125 (14.40%)               |  |  |
| occurrences (all)                                    | 21                              |  |  |
| Fatigue                                              |                                 |  |  |
| subjects affected / exposed                          | 40 / 125 (32.00%)               |  |  |
| occurrences (all)                                    | 43                              |  |  |
| Injection site haematoma                             |                                 |  |  |
| subjects affected / exposed                          | 6 / 125 (4.80%)                 |  |  |
| occurrences (all)                                    | 7                               |  |  |
| Injection site pain                                  |                                 |  |  |
| subjects affected / exposed                          | 14 / 125 (11.20%)               |  |  |
| occurrences (all)                                    | 16                              |  |  |
| Injection site erythema                              |                                 |  |  |
| subjects affected / exposed                          | 12 / 125 (9.60%)                |  |  |
| occurrences (all)                                    | 30                              |  |  |
| Injection site reaction                              |                                 |  |  |
| subjects affected / exposed                          | 10 / 125 (8.00%)                |  |  |
| occurrences (all)                                    | 11                              |  |  |
| Oedema peripheral                                    |                                 |  |  |
| subjects affected / exposed                          | 14 / 125 (11.20%)               |  |  |
| occurrences (all)                                    | 15                              |  |  |
| Uncoded                                              | Additional description: Uncoded |  |  |
| alternative dictionary used: Other                   |                                 |  |  |
| Other                                                |                                 |  |  |
| subjects affected / exposed                          | 16 / 125 (12.80%)               |  |  |
| occurrences (all)                                    | 18                              |  |  |
| Reproductive system and breast disorders             |                                 |  |  |

|                                                                                                                             |                         |  |  |
|-----------------------------------------------------------------------------------------------------------------------------|-------------------------|--|--|
| Breast oedema<br>subjects affected / exposed<br>occurrences (all)                                                           | 7 / 125 (5.60%)<br>7    |  |  |
| Breast pain<br>subjects affected / exposed<br>occurrences (all)                                                             | 7 / 125 (5.60%)<br>7    |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)                | 13 / 125 (10.40%)<br>13 |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                                | 10 / 125 (8.00%)<br>10  |  |  |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)                                     | 7 / 125 (5.60%)<br>7    |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                                                | 7 / 125 (5.60%)<br>7    |  |  |
| Investigations<br>Ejection fraction decreased<br>subjects affected / exposed<br>occurrences (all)                           | 14 / 125 (11.20%)<br>15 |  |  |
| Injury, poisoning and procedural complications<br>Radiation skin injury<br>subjects affected / exposed<br>occurrences (all) | 6 / 125 (4.80%)<br>9    |  |  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                                       | 9 / 125 (7.20%)<br>9    |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                                    | 11 / 125 (8.80%)<br>13  |  |  |
| Dizziness                                                                                                                   |                         |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 14 / 125 (11.20%) |  |  |
| occurrences (all)                               | 14                |  |  |
| Neuropathy peripheral                           |                   |  |  |
| subjects affected / exposed                     | 7 / 125 (5.60%)   |  |  |
| occurrences (all)                               | 7                 |  |  |
| Paraesthesia                                    |                   |  |  |
| subjects affected / exposed                     | 14 / 125 (11.20%) |  |  |
| occurrences (all)                               | 17                |  |  |
| Gastrointestinal disorders                      |                   |  |  |
| Nausea                                          |                   |  |  |
| subjects affected / exposed                     | 16 / 125 (12.80%) |  |  |
| occurrences (all)                               | 18                |  |  |
| Skin and subcutaneous tissue disorders          |                   |  |  |
| Pruritus                                        |                   |  |  |
| subjects affected / exposed                     | 7 / 125 (5.60%)   |  |  |
| occurrences (all)                               | 7                 |  |  |
| Rash                                            |                   |  |  |
| subjects affected / exposed                     | 4 / 125 (3.20%)   |  |  |
| occurrences (all)                               | 7                 |  |  |
| Musculoskeletal and connective tissue disorders |                   |  |  |
| Arthralgia                                      |                   |  |  |
| subjects affected / exposed                     | 24 / 125 (19.20%) |  |  |
| occurrences (all)                               | 24                |  |  |
| Back pain                                       |                   |  |  |
| subjects affected / exposed                     | 8 / 125 (6.40%)   |  |  |
| occurrences (all)                               | 8                 |  |  |
| Muscle spasms                                   |                   |  |  |
| subjects affected / exposed                     | 7 / 125 (5.60%)   |  |  |
| occurrences (all)                               | 7                 |  |  |
| Musculoskeletal Stiffness                       |                   |  |  |
| subjects affected / exposed                     | 8 / 125 (6.40%)   |  |  |
| occurrences (all)                               | 8                 |  |  |
| Myalgia                                         |                   |  |  |
| subjects affected / exposed                     | 25 / 125 (20.00%) |  |  |
| occurrences (all)                               | 25                |  |  |
| Musculoskeletal chest pain                      |                   |  |  |

|                                                                                                                                                                                                   |                                                                    |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                                                       | <p>8 / 125 (6.40%)</p> <p>8</p>                                    |  |  |
| <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                              | <p>9 / 125 (7.20%)</p> <p>10</p>                                   |  |  |
| <p>Infections and infestations</p> <p>Cystitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>8 / 125 (6.40%)</p> <p>9</p> <p>30 / 125 (24.00%)</p> <p>34</p> |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 03 February 2014 | Exclusion criterion 10 (inadequate bone marrow function) was deleted. This criterion is used for (dis)continuation of chemotherapy, not for (dis)continuation of trastuzumab. Safety lab was determined at screening, but bone marrow function was not used for in/exclusion. The sample size was corrected from 150 to 128. Trastuzumab SC vials were added as IMP because vials were used as back-up in case of SID failure. Furthermore, a description on how to handle SID failure was added. Text was added to indicate that also HCP could return the SID to the hospital. Text was added to indicate that the ICF had to be signed within 28 days to first dose. Visit windows were added to Protocol Section 4.4.2.1, and the time point for completion of the questionnaires was clarified and a time window was added to Protocol Section 4.4.7. The option of paper questionnaires was added to Protocol Section 7.3. MRI was deleted as a method for left ventricular ejection fraction (LVEF) measurement because this is only done by echocardiography (ECHO) or multiple gated acquisition (MUGA). Time points for cardiac safety assessments were added to Protocol Section 5.1.2 following addition of an extra schedule of assessments (see below). A schedule of assessment for patients that received 6 cycles of trastuzumab prior to the study was added and time of assessments were corrected throughout the protocol. Further revisions to the schedule of assessments were made to clarify which assessments needed to be done at which time point, and a time window for PK sampling "within 1 day before administration" and a note [t] concerning hematology and chemistry were added. |
| 29 April 2014    | The time point for completion of the questionnaires was clarified and a time window was added in Protocol Section 3.9.4. In inclusion criterion 6, the text 'except for patients in the neo-adjuvant setting' was deleted because this study only included patients in the adjuvant setting, and the text 'in combination with chemotherapy' was added to be compliant with the guidelines for breast cancer therapy. In inclusion criterion 7, LVEF was adjusted from $\geq 55\%$ to $\geq 50\%$ in line with the Dutch guidelines for mamma care "mammacarcinoom richtlijn, 2.0", which states that LVEF needs to be 50%-55% shortly before start of trastuzumab. In inclusion 7 criterion, the text 'Except in case patient received anthracycline treatment previously then documented results within an acceptable limit from a cardiac assessment within 14 days prior to enrolment.' was added. A section on Adverse Events of Special Interest (AESI) was added. In the schedule of assessment, LVEF at Cycle 1 Day 1 was deleted due to the change in inclusion criterion 7; the LVEF occurred at screening within 14 days prior to enrolment for all patients that received anthracycline treatment previously and did not need to be repeated at Cycle 1 Day 1.                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 21 May 2015      | The Multiplex Ligation-dependent Probe Amplification (MLPA) method was added as an additional test to determine HER2 status. The use of hormonal auterine devices (IUDs) was clarified in exclusion criterion 6. The time window for completion of the SF-36 en MASQ questionnaires was clarified (within one week after dosing at Cycles 3 and 9).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported