



## Clinical trial results:

**A randomized, open-label, 2-arm, multicentre, phase III study to evaluate the efficacy and safety of bevacizumab in combination with trastuzumab / docetaxel compared with trastuzumab/docetaxel alone as first line treatment for patients with HER2 positive locally recurrent or metastatic breast cancer**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2006-001365-42 |
| Trial protocol           | AT IT CZ ES GB |
| Global end of trial date |                |

### Results information

|                                |                                                                                                                                                                                                          |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                                                                                                             |
| This version publication date  | 02 June 2016                                                                                                                                                                                             |
| First version publication date | 06 August 2015                                                                                                                                                                                           |
| Version creation reason        | <ul style="list-style-type: none"><li>• Correction of full data set</li></ul> We have performed an internal QC of the record and findings have been identified which need to be rectified in the record. |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | BO20231 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00391092 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                                                                                    |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | F. Hoffmann-La Roche AG                                                                                                                                            |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070                                                                                                                 |
| Public contact               | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, <a href="mailto:global.trial_information@roche.com">global.trial_information@roche.com</a> |
| Scientific contact           | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, <a href="mailto:global.trial_information@roche.com">global.trial_information@roche.com</a> |

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                                       | Interim      |
| Date of interim/final analysis                       | 30 June 2011 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 30 June 2011 |
| Global end of trial reached?                         | No           |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate efficacy and safety of bevacizumab in combination with trastuzumab/docetaxel versus compared with trastuzumab/docetaxel alone as first line treatment.

Protection of trial subjects:

The investigator ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the patient. For EU/EEA countries, the investigator ensured compliance with the EU Clinical Trial Directive (2001/20/EC). In other countries where "Guideline for Good Clinical Practice" existed Roche and the investigators strictly ensured adherence to the stated provisions.

Background therapy: -

Evidence for comparator: -

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 28 September 2006 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety            |
| Long term follow-up duration                              | 1 Months          |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                            |
|--------------------------------------|----------------------------|
| Country: Number of subjects enrolled | Argentina: 1               |
| Country: Number of subjects enrolled | Russian Federation: 90     |
| Country: Number of subjects enrolled | Australia: 26              |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 10 |
| Country: Number of subjects enrolled | Brazil: 43                 |
| Country: Number of subjects enrolled | Canada: 21                 |
| Country: Number of subjects enrolled | Mexico: 10                 |
| Country: Number of subjects enrolled | Romania: 18                |
| Country: Number of subjects enrolled | Turkey: 7                  |
| Country: Number of subjects enrolled | Uruguay: 3                 |
| Country: Number of subjects enrolled | Spain: 14                  |
| Country: Number of subjects enrolled | United Kingdom: 45         |
| Country: Number of subjects enrolled | Austria: 16                |
| Country: Number of subjects enrolled | Czech Republic: 3          |
| Country: Number of subjects enrolled | France: 79                 |
| Country: Number of subjects enrolled | Italy: 38                  |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 424 |
| EEA total number of subjects       | 213 |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                      | 347 |
| From 65 to 84 years                       | 77  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The participants were randomized 1:1 using a block design randomization procedure with stratification (for prior adjuvant/neo-adjuvant taxane, trastuzumab as part of adjuvant treatment versus no trastuzumab, ER/PgR hormone receptor status and measurable disease) to avoid an imbalance of important prognostic factors.

### Period 1

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

Blinding implementation details:

This was an open-label study. However, the Independent Review Committee (IRC) assessment was blinded to treatment assignment.

### Arms

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes                     |
| <b>Arm title</b>             | Trastuzumab + Docetaxel |

Arm description:

Trastuzumab 8 milligrams per kilogram (mg/kg) loading dose administered intravenously on Day 1 of Cycle 1, followed by docetaxel 100 milligrams per square meter (mg/m<sup>2</sup>) on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg and docetaxel at 100 mg/m<sup>2</sup> were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent, and for a minimum of 6 cycles, respectively.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | Trastuzumab     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Participants received 8 mg/kg trastuzumab intravenously on Cycle 1 Day 1, and thereafter 6 mg/kg trastuzumab on Day 1 of each 3-week cycle.

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Docetaxel       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Participants received 100 mg/m<sup>2</sup> docetaxel intravenously on Cycle 1 Day 2, and thereafter on Day 1 of each 3-week cycle.

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Trastuzumab + Bevacizumab + Docetaxel |
|------------------|---------------------------------------|

Arm description:

Trastuzumab 8 mg/kg loading dose administered intravenously on Day 1 of Cycle 1, followed by bevacizumab 15 mg/kg and docetaxel 100 mg/m<sup>2</sup> on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg, bevacizumab 15 mg/kg and docetaxel at 100 mg/m<sup>2</sup> were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Trastuzumab     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Participants received 8 mg/kg trastuzumab intravenously on Cycle 1 Day 1, and thereafter 6 mg/kg trastuzumab on Day 1 of each 3-week cycle.

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Docetaxel       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Participants received 100 mg/m<sup>2</sup> docetaxel intravenously on Cycle 1 Day 2, and thereafter 100 mg/m<sup>2</sup> docetaxel on Day 1 of each 3-week cycle.

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Bevacizumab     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Participants received 15 mg/kg bevacizumab intravenously on Cycle 1 Day 2, and thereafter 15 mg/kg bevacizumab on Day 1 of each 3-week cycle.

| Number of subjects in period 1 | Trastuzumab +<br>Docetaxel | Trastuzumab +<br>Bevacizumab +<br>Docetaxel |
|--------------------------------|----------------------------|---------------------------------------------|
|                                |                            |                                             |
| Started                        | 208                        | 216                                         |
| Received Treatment             | 206                        | 215                                         |
| Completed                      | 0                          | 0                                           |
| Not completed                  | 208                        | 216                                         |
| Death                          | 78                         | 81                                          |
| Lost to follow-up              | 13                         | 18                                          |
| Alive on treatment             | 29                         | 33                                          |
| Alive in follow-up             | 88                         | 84                                          |

## Baseline characteristics

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Trastuzumab + Docetaxel |
|-----------------------|-------------------------|

Reporting group description:

Trastuzumab 8 milligrams per kilogram (mg/kg) loading dose administered intravenously on Day 1 of Cycle 1, followed by docetaxel 100 milligrams per square meter (mg/m<sup>2</sup>) on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg and docetaxel at 100 mg/m<sup>2</sup> were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent, and for a minimum of 6 cycles, respectively.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Trastuzumab + Bevacizumab + Docetaxel |
|-----------------------|---------------------------------------|

Reporting group description:

Trastuzumab 8 mg/kg loading dose administered intravenously on Day 1 of Cycle 1, followed by bevacizumab 15 mg/kg and docetaxel 100 mg/m<sup>2</sup> on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg, bevacizumab 15 mg/kg and docetaxel at 100 mg/m<sup>2</sup> were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent.

| Reporting group values             | Trastuzumab + Docetaxel | Trastuzumab + Bevacizumab + Docetaxel | Total |
|------------------------------------|-------------------------|---------------------------------------|-------|
| Number of subjects                 | 208                     | 216                                   | 424   |
| Age categorical<br>Units: Subjects |                         |                                       |       |

|                                                                         |               |                |     |
|-------------------------------------------------------------------------|---------------|----------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 54<br>± 11.71 | 53.5<br>± 10.9 | -   |
| Gender categorical<br>Units: Subjects                                   |               |                |     |
| Female                                                                  | 208           | 216            | 424 |
| Male                                                                    | 0             | 0              | 0   |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Trastuzumab + Docetaxel               |
| Reporting group description:<br>Trastuzumab 8 milligrams per kilogram (mg/kg) loading dose administered intravenously on Day 1 of Cycle 1, followed by docetaxel 100 milligrams per square meter (mg/m <sup>2</sup> ) on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg and docetaxel at 100 mg/m <sup>2</sup> were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent, and for a minimum of 6 cycles, respectively. |                                       |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Trastuzumab + Bevacizumab + Docetaxel |
| Reporting group description:<br>Trastuzumab 8 mg/kg loading dose administered intravenously on Day 1 of Cycle 1, followed by bevacizumab 15 mg/kg and docetaxel 100 mg/m <sup>2</sup> on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg, bevacizumab 15 mg/kg and docetaxel at 100 mg/m <sup>2</sup> were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent.                                                        |                                       |

### Primary: Progression-Free Survival (PFS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Progression-Free Survival (PFS) |
| End point description:<br>PFS was defined as the time from randomization to time of first documented disease progression (unequivocal progression of existing non-target lesions) or death, whichever occurred first as assessed by Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST v1.0). Primary PFS variable was defined based on the investigators' assessments and the statistical conclusions on the primary efficacy end point were based on investigator assessed PFS. PFS was estimated using Kaplan-Meier methods. Intent-to-treat (ITT) population: All randomized participants, regardless of whether they actually received study treatment or not. |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Primary                         |
| End point timeframe:<br>Every 9 weeks up to Week 36, thereafter every 12 weeks until disease progression (up to the clinical cutoff of 30 June 2011, up to 4.75 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                 |

| End point values                 | Trastuzumab + Docetaxel | Trastuzumab + Bevacizumab + Docetaxel |  |  |
|----------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type               | Reporting group         | Reporting group                       |  |  |
| Number of subjects analysed      | 208                     | 216                                   |  |  |
| Units: months                    |                         |                                       |  |  |
| median (confidence interval 95%) | 13.7 (11.4 to 16.3)     | 16.5 (14.1 to 19.1)                   |  |  |

### Statistical analyses

|                            |                                                                 |
|----------------------------|-----------------------------------------------------------------|
| Statistical analysis title | Progression-Free Survival (PFS)                                 |
| Comparison groups          | Trastuzumab + Bevacizumab + Docetaxel v Trastuzumab + Docetaxel |

|                                         |                        |
|-----------------------------------------|------------------------|
| Number of subjects included in analysis | 424                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.0775               |
| Method                                  | Logrank (unstratified) |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.82                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.65                   |
| upper limit                             | 1.02                   |

## Secondary: Overall Survival (OS)

|                                                                                                                                                                                                                                                                                                                                                                                         |                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                         | Overall Survival (OS) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                  |                       |
| OS was defined as the time from randomization to the date of death, regardless of the cause of death. OS was estimated using Kaplan-Meier methods. ITT population. Here '99999' was used as the upper range of 95% confidence interval (CI) was not calculable due to immature OS data as greater than 50% of participants were censored at the time of clinical cutoff (30 June 2011). |                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                          | Secondary             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                    |                       |
| Every 9 weeks up to Week 36, thereafter every 12 weeks until disease progression (up to the clinical cutoff of 30 June 2011, up to 4.75 years)                                                                                                                                                                                                                                          |                       |

| End point values                 | Trastuzumab + Docetaxel | Trastuzumab + Bevacizumab + Docetaxel |  |  |
|----------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type               | Reporting group         | Reporting group                       |  |  |
| Number of subjects analysed      | 208                     | 216                                   |  |  |
| Units: months                    |                         |                                       |  |  |
| median (confidence interval 95%) | 38.3 (34.3 to 99999)    | 38.5 (32.1 to 99999)                  |  |  |

## Statistical analyses

|                                         |                                                                 |
|-----------------------------------------|-----------------------------------------------------------------|
| Statistical analysis title              | Overall Survival (OS)                                           |
| Comparison groups                       | Trastuzumab + Docetaxel v Trastuzumab + Bevacizumab + Docetaxel |
| Number of subjects included in analysis | 424                                                             |
| Analysis specification                  | Pre-specified                                                   |
| Analysis type                           | superiority                                                     |
| P-value                                 | = 0.9543                                                        |
| Method                                  | Logrank                                                         |
| Parameter estimate                      | Hazard ratio (HR)                                               |
| Point estimate                          | 1.01                                                            |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.74    |
| upper limit         | 1.38    |

### Secondary: Percentage of Participants With a Best Overall Response (OR) of Confirmed Complete Response (CR) or Partial Response (PR) in Participants with Measurable Disease at Baseline

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                               |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Percentage of Participants With a Best Overall Response (OR) of Confirmed Complete Response (CR) or Partial Response (PR) in Participants with Measurable Disease at Baseline |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                               |
| Best OR was assessed using RECIST v1.0 criteria. Participants were classified as responders if their best OR was either confirmed CR (disappearance of all target lesions) or confirmed PR (at least a 30% decrease in the sum of the longest diameter [LD] of target lesions, taking as reference the baseline sum LD). Participants without any post-baseline assessments were regarded as non-responders. The 95% CI for the one sample binomial using Pearson-Clopper method. ITT population. |                                                                                                                                                                               |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Secondary                                                                                                                                                                     |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                               |
| Every 9 weeks up to Week 36, thereafter every 12 weeks until disease progression (up to clinical data cutoff of 30 June 2011, up to 4.75 years)                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                               |

| End point values                  | Trastuzumab + Docetaxel | Trastuzumab + Bevacizumab + Docetaxel |  |  |
|-----------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type                | Reporting group         | Reporting group                       |  |  |
| Number of subjects analysed       | 176 <sup>[1]</sup>      | 183 <sup>[2]</sup>                    |  |  |
| Units: Percentage of participants |                         |                                       |  |  |
| number (confidence interval 95%)  |                         |                                       |  |  |
| Responders                        | 69.9 (62.5 to 76.6)     | 74.3 (67.4 to 80.5)                   |  |  |

Notes:

[1] - Only participants with measurable disease at baseline were included in the analysis.

[2] - only participants with measurable disease at baseline were included in the analysis.

### Statistical analyses

|                                         |                                                                 |
|-----------------------------------------|-----------------------------------------------------------------|
| Statistical analysis title              | % of Participants With Confirmed CR and PR                      |
| Comparison groups                       | Trastuzumab + Docetaxel v Trastuzumab + Bevacizumab + Docetaxel |
| Number of subjects included in analysis | 359                                                             |
| Analysis specification                  | Pre-specified                                                   |
| Analysis type                           | superiority                                                     |
| P-value                                 | = 0.3492                                                        |
| Method                                  | Chi-squared                                                     |
| Parameter estimate                      | Difference in Response rates                                    |
| Point estimate                          | 4.43                                                            |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -5.2    |
| upper limit         | 14      |

## Secondary: Duration of Response (DR)

|                 |                           |
|-----------------|---------------------------|
| End point title | Duration of Response (DR) |
|-----------------|---------------------------|

End point description:

DR was defined as the time when response (CR or PR per RECIST v1.0) was first documented to the date of disease progression per RECIST v1.0 (unequivocal progression of existing non-target lesions) or death. ITT population.

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

End point timeframe:

Every 9 weeks up to Week 36, thereafter every 12 weeks until disease progression (up to clinical cutoff of 30 June 2011, up to 4.75 years)

| End point values                 | Trastuzumab + Docetaxel | Trastuzumab + Bevacizumab + Docetaxel |  |  |
|----------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type               | Reporting group         | Reporting group                       |  |  |
| Number of subjects analysed      | 123 <sup>[3]</sup>      | 136 <sup>[4]</sup>                    |  |  |
| Units: months                    |                         |                                       |  |  |
| median (confidence interval 95%) | 11.4 (9.1 to 13.2)      | 14.6 (12 to 17.1)                     |  |  |

Notes:

[3] - Only participants with a best OR of CR or PR were included in the analysis.

[4] - Only participants with a best OR of CR or PR were included in the analysis.

## Statistical analyses

|                                         |                                                                 |
|-----------------------------------------|-----------------------------------------------------------------|
| Statistical analysis title              | Duration of Response (DR)                                       |
| Comparison groups                       | Trastuzumab + Docetaxel v Trastuzumab + Bevacizumab + Docetaxel |
| Number of subjects included in analysis | 259                                                             |
| Analysis specification                  | Pre-specified                                                   |
| Analysis type                           | superiority                                                     |
| Parameter estimate                      | Hazard ratio (HR)                                               |
| Point estimate                          | 0.74                                                            |
| Confidence interval                     |                                                                 |
| level                                   | 95 %                                                            |
| sides                                   | 2-sided                                                         |
| lower limit                             | 0.56                                                            |
| upper limit                             | 0.98                                                            |

## Secondary: Time to Treatment Failure (TTF)

|                                                                                                                                                                                                                                                                                                                                                                                                      |                                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                      | Time to Treatment Failure (TTF) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                               |                                 |
| TTF was defined as the time between randomization and date of disease progression (per RECIST v1.0; unequivocal progression of existing non-target lesions), death, or withdrawal of treatment due to adverse events, withdrawal of informed consent, insufficient therapeutic response, refusal of treatment/failure to co-operate, or failure to return, whichever occurred first. ITT population. |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                       | Secondary                       |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                 |                                 |
| Every 9 weeks up to Week 36, thereafter every 12 weeks until disease progression (up to clinical cutoff of 30 June 2011, up to 4.75 years)                                                                                                                                                                                                                                                           |                                 |

| End point values                 | Trastuzumab + Docetaxel | Trastuzumab + Bevacizumab + Docetaxel |  |  |
|----------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type               | Reporting group         | Reporting group                       |  |  |
| Number of subjects analysed      | 208                     | 216                                   |  |  |
| Units: months                    |                         |                                       |  |  |
| median (confidence interval 95%) | 7.7 (6.3 to 8.6)        | 9.8 (7.9 to 10.9)                     |  |  |

## Statistical analyses

|                                         |                                                                 |
|-----------------------------------------|-----------------------------------------------------------------|
| Statistical analysis title              | Time to Treatment Failure (TTF)                                 |
| Comparison groups                       | Trastuzumab + Docetaxel v Trastuzumab + Bevacizumab + Docetaxel |
| Number of subjects included in analysis | 424                                                             |
| Analysis specification                  | Pre-specified                                                   |
| Analysis type                           | superiority                                                     |
| P-value                                 | = 0.5392                                                        |
| Method                                  | Logrank                                                         |
| Parameter estimate                      | Hazard ratio (HR)                                               |
| Point estimate                          | 0.94                                                            |
| Confidence interval                     |                                                                 |
| level                                   | 95 %                                                            |
| sides                                   | 2-sided                                                         |
| lower limit                             | 0.76                                                            |
| upper limit                             | 1.15                                                            |

## Secondary: Functional Assessment of Cancer Therapy-Generic (FACT-G) and Functional Assessment of Cancer Therapy-Breast (FACT-B) Subscale Scores

|                 |                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Functional Assessment of Cancer Therapy-Generic (FACT-G) and Functional Assessment of Cancer Therapy-Breast (FACT-B) Subscale Scores |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|

### End point description:

FACT-G is core questionnaire of Functional Assessment of Chronic Illness Therapy (FACIT) measurement system to evaluate quality of life (QoL) in cancer population. FACT-G consisted of 27 questions grouped in 4 domains of general Health-Related QoL (HRQoL): Physical Well-being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB) and Functional Well-Being (FWB); each

ranged from 0 (not at all) to 4 (very much). FACT-G ranged between 0-108. Since questions could be reversed coded, as appropriate, before calculating FACT-G, 0 and 108 could be considered worst and best health states. FACT-B is used for assessment of HRQoL in participants with breast cancer. It consists of 36 items, summarized to 5 subscales: 7 items for each physical, functional, social/family; all 3 ranged from 0-28, emotional (6 items) ranged from 0-24, and breast cancer subscale (9 items) ranged from 0-36. All single-item measures ranges from 0-144. High score represents a better QoL. ITT population.

|                                                                                                                                                                 |           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                                                                  | Secondary |
| End point timeframe:                                                                                                                                            |           |
| Baseline, Cycles 3, 5, 11, and post progressive disease (PD; 14 to 28 days after disease progression [up to clinical cutoff of 30 June 2011, up to 4.75 years]) |           |

| End point values                            | Trastuzumab + Docetaxel | Trastuzumab + Bevacizumab + Docetaxel |  |  |
|---------------------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type                          | Reporting group         | Reporting group                       |  |  |
| Number of subjects analysed                 | 173 <sup>[5]</sup>      | 189 <sup>[6]</sup>                    |  |  |
| Units: units on a scale                     |                         |                                       |  |  |
| arithmetic mean (standard deviation)        |                         |                                       |  |  |
| Physical Well-Being: Baseline (n=173,189)   | 21.2 (± 5.74)           | 21.47 (± 5.07)                        |  |  |
| Social Well-Being: Baseline (n=173,189)     | 20.59 (± 5.75)          | 20.88 (± 5.77)                        |  |  |
| Emotional Well-Being: Baseline (n=173,189)  | 14.95 (± 4.95)          | 15.54 (± 4.44)                        |  |  |
| Functional Well-Being: Baseline (n=173,189) | 16.34 (± 5.83)          | 16.36 (± 5.57)                        |  |  |
| Total FACT-G Score: Baseline (n=173,189)    | 73.3 (± 16.6)           | 74.49 (± 14.5)                        |  |  |
| Breast Specific: Baseline (n=173,189)       | 21.67 (± 6.43)          | 22.84 (± 5.85)                        |  |  |
| Total FACT-B Score: Baseline (n=173,189)    | 94.97 (± 20.5)          | 97.46 (± 17.71)                       |  |  |
| Trial Outcome Index: Baseline (n=173,189)   | 59.54 (± 14.03)         | 60.85 (± 12.61)                       |  |  |
| Physical Well-Being: Cycle 3 (n=145,173)    | 20.19 (± 4.89)          | 19.96 (± 5.05)                        |  |  |
| Social Well-Being: Cycle 3 (n=145,173)      | 20.64 (± 5.32)          | 21.19 (± 5.44)                        |  |  |
| Emotional Well-Being: Cycle 3 (n=145,173)   | 16.47 (± 4.19)          | 16.7 (± 4.36)                         |  |  |
| Functional Well-Being: Cycle 3 (n=145,173)  | 15.43 (± 5.33)          | 16.2 (± 5.22)                         |  |  |
| Total FACT-G Score: Cycle 3 (n=145,173)     | 72.94 (± 14.81)         | 74.05 (± 14.35)                       |  |  |
| Breast Specific: Cycle 3 (n=145,173)        | 22.29 (± 5.78)          | 23.17 (± 5.34)                        |  |  |
| Total FACT-B Score: Cycle 3 (n=145,173)     | 95.26 (± 18.52)         | 97.23 (± 17.81)                       |  |  |
| Trial Outcome Index: Cycle 3 (n=145,173)    | 58.04 (± 12.8)          | 59.33 (± 12.49)                       |  |  |
| Physical Well-Being: Cycle 5 (n=139,166)    | 19.51 (± 4.83)          | 19.67 (± 4.56)                        |  |  |
| Social Well-Being: Cycle 5 (n=139,166)      | 19.36 (± 5.26)          | 20.68 (± 4.92)                        |  |  |
| Emotional Well-Being: Cycle 5 (n=139,166)   | 16.05 (± 4.44)          | 17.07 (± 4.3)                         |  |  |
| Functional Well-Being: Cycle 5 (n=139,166)  | 14.81 (± 5.45)          | 15.78 (± 4.77)                        |  |  |
| Total FACT-G Score: Cycle 5 (n=139,166)     | 69.78 (± 15.04)         | 73.21 (± 12.49)                       |  |  |

|                                              |                 |                  |  |  |
|----------------------------------------------|-----------------|------------------|--|--|
| Breast Specific: Cycle 5 (n=139, 166)        | 21.65 (± 5.83)  | 23.15 (± 4.9)    |  |  |
| Total FACT-B Score: Cycle 5 (n=139, 166)     | 91.43 (± 18.81) | 96.36 (± 15.63)  |  |  |
| Trial Outcome Index: Cycle 5 (n=139, 166)    | 55.99 (± 13.09) | 58.59 (± 11.01)  |  |  |
| Physical Well-Being: Cycle 11 (n=100, 133)   | 21.71 (± 4.54)  | 21.56 (± 4.53)   |  |  |
| Social Well-Being: Cycle 11 (n=100, 133)     | 19.71 (± 5.74)  | 20.78 (± 4.92)   |  |  |
| Emotional Well-Being: Cycle 11 (n=100, 133)  | 15.96 (± 4.5)   | 17.46 (± 3.7)    |  |  |
| Functional Well-Being: Cycle 11 (n=100, 133) | 16.25 (± 5.16)  | 16.98 (± 4.92)   |  |  |
| Total FACT-G Score: Cycle 11 (n=100, 133)    | 73.26 (± 15.24) | 76.55 (± 13.56)  |  |  |
| Breast Specific: Cycle 11 (n=100, 133)       | 21.29 (± 5.55)  | 23.8 (± 4.92)    |  |  |
| Total FACT-B Score: Cycle 11 (n=100, 133)    | 94.57 (± 18.58) | 100.43 (± 16.97) |  |  |
| Trial Outcome Index: Cycle 11 (n=100, 133)   | 59.19 (± 12)    | 62.34 (± 11.79)  |  |  |
| Physical Well-Being: Post PD (n=33, 39)      | 19.94 (± 4.99)  | 20.35 (± 5.37)   |  |  |
| Social Well-Being: Post PD (n=33, 39)        | 19.02 (± 5.61)  | 19.68 (± 4.77)   |  |  |
| Emotional Well-Being: Post PD (n=33, 39)     | 14.76 (± 4.83)  | 14.77 (± 4.64)   |  |  |
| Functional Well-Being: Post PD (n=33, 39)    | 14.13 (± 5.57)  | 15.08 (± 5.16)   |  |  |
| Total FACT-G Score: Post PD (n=33, 39)       | 67.84 (± 14.21) | 70.04 (± 15.08)  |  |  |
| Breast Specific: Post PD (n=33, 39)          | 22.9 (± 4.48)   | 22.87 (± 5.14)   |  |  |
| Total FACT-B Score: Post PD (n=33, 39)       | 90.74 (± 16.59) | 92.92 (± 18.47)  |  |  |
| Trial Outcome Index: Post PD (n=33, 39)      | 56.97 (± 11.16) | 58.47 (± 12.43)  |  |  |

Notes:

[5] - n (number) = number of participants assessed for the given parameter at the specified visit.

[6] - n (number) = number of participants assessed for the given parameter at the specified visit.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline for FACT-G and FACT-B

|                 |                                            |
|-----------------|--------------------------------------------|
| End point title | Change From Baseline for FACT-G and FACT-B |
|-----------------|--------------------------------------------|

End point description:

FACT-G is core questionnaire of FACIT measurement system to evaluate QoL in cancer population. FACT-G consisted of 27 questions grouped in 4 domains of general HRQoL: PWB, SWB, EWB and FWB; each ranged from 0 (not at all) to 4 (very much). FACT-G ranged between 0-108. Since questions could be reversed coded, as appropriate, before calculating FACT-G, 0 and 108 could be considered worst and best health states. FACT -B is used for assessment of HRQoL in participants with breast cancer. It consists of 36 items, summarized to 5 subscales: 7 items for each physical, functional, social/family; all 3 ranged from 0-28, emotional (6 items) ranged from 0-24, and breast cancer subscale (9 items) ranged from 0-36. All single-item measures ranges from 0-144. High score represents a better QoL. ITT population.

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

End point timeframe:

Baseline, Cycles 3, 5, 11, and post PD (14 to 28 days after disease progression [up to clinical cutoff of 30 June 2011, up to 4.75 years])

| End point values                             | Trastuzumab + Docetaxel | Trastuzumab + Bevacizumab + Docetaxel |  |  |
|----------------------------------------------|-------------------------|---------------------------------------|--|--|
| Subject group type                           | Reporting group         | Reporting group                       |  |  |
| Number of subjects analysed                  | 145 <sup>[7]</sup>      | 173 <sup>[8]</sup>                    |  |  |
| Units: units on a scale                      |                         |                                       |  |  |
| arithmetic mean (standard deviation)         |                         |                                       |  |  |
| Physical Well-Being: Cycle 3 (n=145,173)     | -1.01 (± 7.54)          | -1.51 (± 7.16)                        |  |  |
| Social Well-Being: Cycle 3 (n=145,173)       | 0.05 (± 7.83)           | 0.32 (± 7.93)                         |  |  |
| Emotional Well-Being: Cycle 3 (n=145,173)    | 1.52 (± 6.49)           | 1.16 (± 6.22)                         |  |  |
| Functional Well-Being: Cycle 3 (n=145, 173)  | -0.91 (± 7.9)           | -0.16 (± 7.63)                        |  |  |
| Total FACT-G Score: Cycle 3 (n=145,173)      | -0.36 (± 22.25)         | -0.44 (± 20.4)                        |  |  |
| Breast Specific: Cycle 3 (n=145,173)         | 0.61 (± 8.65)           | 0.34 (± 7.92)                         |  |  |
| Total FACT-B Score: Cycle 3 (n=145,173)      | 0.29 (± 27.63)          | -0.24 (± 25.12)                       |  |  |
| Trial Outcome Index: Cycle 3 (n=145,173)     | -1.5 (± 18.99)          | -1.52 (± 17.75)                       |  |  |
| Physical Well-Being: Cycle 5 (n=139, 166)    | -1.69 (± 7.5)           | -1.8 (± 6.82)                         |  |  |
| Social Well-Being: Cycle 5 (n=139, 166)      | -1.23 (± 7.79)          | -0.2 (± 7.58)                         |  |  |
| Emotional Well-Being: Cycle 5 (n=139, 166)   | 1.09 (± 6.65)           | 1.53 (± 6.18)                         |  |  |
| Functional Well-Being: Cycle 5 (n=139, 166)  | -1.53 (± 7.98)          | -0.58 (± 7.33)                        |  |  |
| Total FACT-G Score: Cycle 5 (n=139, 166)     | -3.53 (± 22.4)          | -1.28 (± 19.14)                       |  |  |
| Breast Specific: Cycle 5 (n=139, 166)        | -0.03 (± 8.68)          | 0.31 (± 7.63)                         |  |  |
| Total FACT-B Score: Cycle 5 (n=139, 166)     | -3.55 (± 27.82)         | -1.1 (± 23.62)                        |  |  |
| Trial Outcome Index: Cycle 5 (n=139,166)     | -3.55 (± 19.19)         | -2.26 (± 16.74)                       |  |  |
| Physical Well-Being: Cycle 11 (n=100, 133)   | 0.51 (± 7.32)           | 0.09 (± 6.8)                          |  |  |
| Social Well-Being: Cycle 11 (n=100, 133)     | -0.89 (± 8.13)          | -0.1 (± 7.58)                         |  |  |
| Emotional Well-Being: Cycle 11 (n=100, 133)  | 1 (± 6.69)              | 1.92 (± 5.78)                         |  |  |
| Functional Well-Being: Cycle 11 (n=100, 133) | -0.09 (± 7.79)          | 0.62 (± 7.43)                         |  |  |
| Total FACT-G Score: Cycle 11 (n=100, 133)    | -0.05 (± 22.54)         | 2.06 (± 19.85)                        |  |  |
| Breast Specific: Cycle 11 (n=100, 133)       | -0.38 (± 8.49)          | 0.96 (± 7.64)                         |  |  |
| Total FACT-B Score: Cycle 11 (n=100, 133)    | -0.41 (± 27.67)         | 2.97 (± 24.53)                        |  |  |
| Trial Outcome Index: Cycle 11 (n=100, 133)   | -0.35 (± 18.46)         | 1.49 (± 17.26)                        |  |  |
| Physical Well-Being: Post PD (n=33, 39)      | -1.25 (± 7.61)          | -1.12 (± 7.39)                        |  |  |
| Social Well-Being: Post PD (n=33, 39)        | -1.58 (± 8.03)          | -1.19 (± 7.48)                        |  |  |
| Emotional Well-Being: Post PD (n=33, 39)     | -0.2 (± 6.92)           | -0.78 (± 6.42)                        |  |  |

|                                           |                 |                 |  |  |
|-------------------------------------------|-----------------|-----------------|--|--|
| Functional Well-Being: Post PD (n=33, 39) | -2.22 (± 8.06)  | -1.28 (± 7.59)  |  |  |
| Total FACT-G Score: Post PD (n=33, 39)    | -5.46 (± 21.85) | -4.44 (± 20.92) |  |  |
| Breast Specific: Post PD (n=33, 39)       | 1.22 (± 7.84)   | 0.03 (± 7.79)   |  |  |
| Total FACT-B Score: Post PD (n=33, 39)    | -4.23 (± 26.37) | -4.55 (± 25.59) |  |  |
| Trial Outcome Index: Post PD (n=33, 39)   | -2.57 (± 17.92) | -2.38 (± 17.7)  |  |  |

Notes:

[7] - n (number) = number of participants assessed for the given parameter at the specified visit.

[8] - n (number) = number of participants assessed for the given parameter at the specified visit.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From time of first drug intake up to 28 days after last dose study treatment (up to 4.75 years)

Adverse event reporting additional description:

Safety population included all participants who had received at least 1 dose of the trial medication, whether withdrawn prematurely or not.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Trastuzumab + Docetaxel |
|-----------------------|-------------------------|

Reporting group description:

Trastuzumab 8 mg/kg loading dose administered intravenously on Day 1 of Cycle 1, followed by docetaxel 100 mg/m<sup>2</sup> on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg and docetaxel at 100 mg/m<sup>2</sup> were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent, and for a minimum of 6 cycles, respectively.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Trastuzumab + Bevacizumab + Docetaxel |
|-----------------------|---------------------------------------|

Reporting group description:

Trastuzumab 8 mg/kg loading dose administered intravenously on Day 1 of Cycle 1, followed by bevacizumab 15 mg/kg and docetaxel 100 mg/m<sup>2</sup> on Day 2 of Cycle 1. Then a maintenance dose of trastuzumab at 6 mg/kg, bevacizumab 15 mg/kg and docetaxel at 100 mg/m<sup>2</sup> were administered intravenously on Day 1 of each 3-weekly cycle until disease progression, unacceptable toxicity (requiring discontinuation of study treatment), or withdrawal of participant's consent.

| Serious adverse events                                              | Trastuzumab + Docetaxel | Trastuzumab + Bevacizumab + Docetaxel |  |
|---------------------------------------------------------------------|-------------------------|---------------------------------------|--|
| Total subjects affected by serious adverse events                   |                         |                                       |  |
| subjects affected / exposed                                         | 63 / 206 (30.58%)       | 72 / 215 (33.49%)                     |  |
| number of deaths (all causes)                                       | 78                      | 81                                    |  |
| number of deaths resulting from adverse events                      |                         |                                       |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                                       |  |
| Thyroid cancer                                                      |                         |                                       |  |
| subjects affected / exposed                                         | 1 / 206 (0.49%)         | 0 / 215 (0.00%)                       |  |
| occurrences causally related to treatment / all                     | 0 / 1                   | 0 / 0                                 |  |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                                 |  |
| Vascular disorders                                                  |                         |                                       |  |
| Circulatory collapse                                                |                         |                                       |  |
| subjects affected / exposed                                         | 0 / 206 (0.00%)         | 1 / 215 (0.47%)                       |  |
| occurrences causally related to treatment / all                     | 0 / 0                   | 0 / 1                                 |  |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                                 |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| Hypertension                                         |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 2 / 215 (0.93%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hypertensive crisis                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Jugular vein thrombosis                              |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vena cava thrombosis                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia                                             |                 |                 |  |
| subjects affected / exposed                          | 1 / 206 (0.49%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                                    |                 |                 |  |
| subjects affected / exposed                          | 2 / 206 (0.97%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General physical health deterioration                |                 |                 |  |
| subjects affected / exposed                          | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Pyrexia                                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 206 (0.97%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Performance status decreased                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malaise                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Anaphylactic reaction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypersensitivity                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Bartholinitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast discharge                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Female genital tract fistula                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 206 (0.97%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 3 / 215 (1.40%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute pulmonary oedema                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 206 (0.97%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cough                                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysphonia                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Bipolar I disorder                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychotic disorder                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| General physical condition abnormal             |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Comminuted fracture                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infusion related reaction                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fracture                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular access complication                    |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wrist fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Arrhythmia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 2 / 215 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiomyopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery stenosis                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery occlusion                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mitral valve incompetence                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery thrombosis                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular dysfunction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Convulsion                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Leukopenia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile neutropenia                             |                 |                 |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 14 / 206 (6.80%) | 18 / 215 (8.37%) |  |
| occurrences causally related to treatment / all | 14 / 14          | 18 / 20          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neutropenia                                     |                  |                  |  |
| subjects affected / exposed                     | 9 / 206 (4.37%)  | 6 / 215 (2.79%)  |  |
| occurrences causally related to treatment / all | 9 / 9            | 6 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anaemia                                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 206 (0.49%)  | 1 / 215 (0.47%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Thrombocytopenia                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 206 (0.49%)  | 0 / 215 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 206 (1.94%)  | 6 / 215 (2.79%)  |  |
| occurrences causally related to treatment / all | 3 / 4            | 4 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 206 (0.00%)  | 3 / 215 (1.40%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 3 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal fistula                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 206 (0.00%)  | 1 / 215 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 206 (0.49%)  | 0 / 215 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal wall haematoma                        |                  |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aphthous stomatitis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer perforation                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enteritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal haemorrhage                              |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stomatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal perforation                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic vein thrombosis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholestasis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatocellular injury                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Exfoliative rash                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue           |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| disorders                                       |                 |                 |  |
| Musculoskeletal chest pain                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pathological fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Neutropenic sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 206 (1.46%) | 6 / 215 (2.79%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 6 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic infection                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 206 (0.97%) | 4 / 215 (1.86%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal Abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 4 / 215 (1.86%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 2 / 215 (0.93%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 206 (1.46%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 206 (0.97%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 2 / 215 (0.93%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess soft tissue                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina gangrenous                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis bacterial                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocarditis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis C                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mastitis                                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphangitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 206 (0.49%) | 0 / 215 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Viral infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 206 (0.00%) | 1 / 215 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Trastuzumab + Docetaxel | Trastuzumab + Bevacizumab + Docetaxel |  |
|-------------------------------------------------------|-------------------------|---------------------------------------|--|
| Total subjects affected by non-serious adverse events |                         |                                       |  |
| subjects affected / exposed                           | 198 / 206 (96.12%)      | 202 / 215 (93.95%)                    |  |
| Vascular disorders                                    |                         |                                       |  |
| Hypertension                                          |                         |                                       |  |
| subjects affected / exposed                           | 27 / 206 (13.11%)       | 79 / 215 (36.74%)                     |  |
| occurrences (all)                                     | 41                      | 115                                   |  |
| Hot flush                                             |                         |                                       |  |
| subjects affected / exposed                           | 16 / 206 (7.77%)        | 12 / 215 (5.58%)                      |  |
| occurrences (all)                                     | 19                      | 15                                    |  |
| Lymphoedema                                           |                         |                                       |  |

|                                                                            |                          |                          |  |
|----------------------------------------------------------------------------|--------------------------|--------------------------|--|
| subjects affected / exposed<br>occurrences (all)                           | 17 / 206 (8.25%)<br>17   | 8 / 215 (3.72%)<br>8     |  |
| Flushing<br>subjects affected / exposed<br>occurrences (all)               | 10 / 206 (4.85%)<br>19   | 12 / 215 (5.58%)<br>20   |  |
| General disorders and administration<br>site conditions                    |                          |                          |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)               | 76 / 206 (36.89%)<br>154 | 75 / 215 (34.88%)<br>139 |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                | 48 / 206 (23.30%)<br>87  | 69 / 215 (32.09%)<br>183 |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)      | 72 / 206 (34.95%)<br>113 | 37 / 215 (17.21%)<br>43  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                | 41 / 206 (19.90%)<br>53  | 51 / 215 (23.72%)<br>82  |  |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all) | 18 / 206 (8.74%)<br>31   | 17 / 215 (7.91%)<br>36   |  |
| Spinal pain<br>subjects affected / exposed<br>occurrences (all)            | 4 / 206 (1.94%)<br>4     | 11 / 215 (5.12%)<br>13   |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                 | 11 / 206 (5.34%)<br>12   | 15 / 215 (6.98%)<br>18   |  |
| Immune system disorders                                                    |                          |                          |  |
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)       | 14 / 206 (6.80%)<br>19   | 10 / 215 (4.65%)<br>12   |  |
| Respiratory, thoracic and mediastinal<br>disorders                         |                          |                          |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                  | 43 / 206 (20.87%)<br>65  | 43 / 215 (20.00%)<br>55  |  |
| Epistaxis                                                                  |                          |                          |  |

|                                                                                        |                         |                           |  |
|----------------------------------------------------------------------------------------|-------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                       | 35 / 206 (16.99%)<br>59 | 109 / 215 (50.70%)<br>251 |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)                        | 18 / 206 (8.74%)<br>31  | 26 / 215 (12.09%)<br>36   |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                           | 46 / 206 (22.33%)<br>61 | 36 / 215 (16.74%)<br>44   |  |
| Dysphonia<br>subjects affected / exposed<br>occurrences (all)                          | 8 / 206 (3.88%)<br>8    | 21 / 215 (9.77%)<br>24    |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                 | 13 / 206 (6.31%)<br>19  | 26 / 215 (12.09%)<br>39   |  |
| Respiratory disorder<br>subjects affected / exposed<br>occurrences (all)               | 8 / 206 (3.88%)<br>9    | 11 / 215 (5.12%)<br>18    |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 21 / 206 (10.19%)<br>24 | 19 / 215 (8.84%)<br>34    |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)                         | 15 / 206 (7.28%)<br>16  | 13 / 215 (6.05%)<br>15    |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                            | 16 / 206 (7.77%)<br>17  | 12 / 215 (5.58%)<br>13    |  |
| Investigations<br>Weight decreased<br>subjects affected / exposed<br>occurrences (all) | 6 / 206 (2.91%)<br>6    | 20 / 215 (9.30%)<br>22    |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                   | 13 / 206 (6.31%)<br>14  | 8 / 215 (3.72%)<br>8      |  |
| Cardiac disorders                                                                      |                         |                           |  |

|                                                                                   |                          |                          |  |
|-----------------------------------------------------------------------------------|--------------------------|--------------------------|--|
| Left ventricular dysfunction<br>subjects affected / exposed<br>occurrences (all)  | 17 / 206 (8.25%)<br>20   | 24 / 215 (11.16%)<br>28  |  |
| Nervous system disorders                                                          |                          |                          |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                      | 40 / 206 (19.42%)<br>67  | 66 / 215 (30.70%)<br>129 |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | 52 / 206 (25.24%)<br>73  | 46 / 215 (21.40%)<br>71  |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                  | 28 / 206 (13.59%)<br>36  | 37 / 215 (17.21%)<br>40  |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                     | 32 / 206 (15.53%)<br>47  | 37 / 215 (17.21%)<br>60  |  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)         | 18 / 206 (8.74%)<br>21   | 22 / 215 (10.23%)<br>29  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                     | 16 / 206 (7.77%)<br>22   | 14 / 215 (6.51%)<br>18   |  |
| Blood and lymphatic system disorders                                              |                          |                          |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                   | 51 / 206 (24.76%)<br>108 | 44 / 215 (20.47%)<br>76  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                       | 24 / 206 (11.65%)<br>28  | 16 / 215 (7.44%)<br>20   |  |
| Ear and labyrinth disorders                                                       |                          |                          |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                       | 13 / 206 (6.31%)<br>17   | 3 / 215 (1.40%)<br>3     |  |
| Eye disorders                                                                     |                          |                          |  |
| Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)         | 59 / 206 (28.64%)<br>75  | 75 / 215 (34.88%)<br>88  |  |

|                             |                   |                    |  |
|-----------------------------|-------------------|--------------------|--|
| Dry eye                     |                   |                    |  |
| subjects affected / exposed | 6 / 206 (2.91%)   | 12 / 215 (5.58%)   |  |
| occurrences (all)           | 6                 | 13                 |  |
| Conjunctivitis              |                   |                    |  |
| subjects affected / exposed | 9 / 206 (4.37%)   | 22 / 215 (10.23%)  |  |
| occurrences (all)           | 14                | 25                 |  |
| Gastrointestinal disorders  |                   |                    |  |
| Diarrhoea                   |                   |                    |  |
| subjects affected / exposed | 85 / 206 (41.26%) | 107 / 215 (49.77%) |  |
| occurrences (all)           | 158               | 265                |  |
| Stomatitis                  |                   |                    |  |
| subjects affected / exposed | 61 / 206 (29.61%) | 95 / 215 (44.19%)  |  |
| occurrences (all)           | 95                | 182                |  |
| Nausea                      |                   |                    |  |
| subjects affected / exposed | 76 / 206 (36.89%) | 82 / 215 (38.14%)  |  |
| occurrences (all)           | 163               | 187                |  |
| Constipation                |                   |                    |  |
| subjects affected / exposed | 47 / 206 (22.82%) | 54 / 215 (25.12%)  |  |
| occurrences (all)           | 65                | 88                 |  |
| Dyspepsia                   |                   |                    |  |
| subjects affected / exposed | 18 / 206 (8.74%)  | 34 / 215 (15.81%)  |  |
| occurrences (all)           | 26                | 58                 |  |
| Vomiting                    |                   |                    |  |
| subjects affected / exposed | 37 / 206 (17.96%) | 42 / 215 (19.53%)  |  |
| occurrences (all)           | 72                | 60                 |  |
| Abdominal pain              |                   |                    |  |
| subjects affected / exposed | 15 / 206 (7.28%)  | 27 / 215 (12.56%)  |  |
| occurrences (all)           | 20                | 45                 |  |
| Abdominal pain upper        |                   |                    |  |
| subjects affected / exposed | 24 / 206 (11.65%) | 23 / 215 (10.70%)  |  |
| occurrences (all)           | 33                | 32                 |  |
| Haemorrhoids                |                   |                    |  |
| subjects affected / exposed | 8 / 206 (3.88%)   | 22 / 215 (10.23%)  |  |
| occurrences (all)           | 13                | 35                 |  |
| Toothache                   |                   |                    |  |

|                                             |                    |                    |  |
|---------------------------------------------|--------------------|--------------------|--|
| subjects affected / exposed                 | 7 / 206 (3.40%)    | 12 / 215 (5.58%)   |  |
| occurrences (all)                           | 7                  | 24                 |  |
| Gastrooesophageal reflux disease            |                    |                    |  |
| subjects affected / exposed                 | 11 / 206 (5.34%)   | 8 / 215 (3.72%)    |  |
| occurrences (all)                           | 19                 | 17                 |  |
| Gingival bleeding                           |                    |                    |  |
| subjects affected / exposed                 | 1 / 206 (0.49%)    | 15 / 215 (6.98%)   |  |
| occurrences (all)                           | 2                  | 26                 |  |
| Rectal haemorrhage                          |                    |                    |  |
| subjects affected / exposed                 | 1 / 206 (0.49%)    | 10 / 215 (4.65%)   |  |
| occurrences (all)                           | 1                  | 14                 |  |
| Skin and subcutaneous tissue disorders      |                    |                    |  |
| Alopecia                                    |                    |                    |  |
| subjects affected / exposed                 | 141 / 206 (68.45%) | 135 / 215 (62.79%) |  |
| occurrences (all)                           | 142                | 142                |  |
| Rash                                        |                    |                    |  |
| subjects affected / exposed                 | 41 / 206 (19.90%)  | 37 / 215 (17.21%)  |  |
| occurrences (all)                           | 58                 | 52                 |  |
| Palmar-plantar erythrodysaesthesia syndrome |                    |                    |  |
| subjects affected / exposed                 | 26 / 206 (12.62%)  | 27 / 215 (12.56%)  |  |
| occurrences (all)                           | 32                 | 34                 |  |
| Nail disorder                               |                    |                    |  |
| subjects affected / exposed                 | 59 / 206 (28.64%)  | 68 / 215 (31.63%)  |  |
| occurrences (all)                           | 65                 | 74                 |  |
| Dry skin                                    |                    |                    |  |
| subjects affected / exposed                 | 25 / 206 (12.14%)  | 28 / 215 (13.02%)  |  |
| occurrences (all)                           | 29                 | 30                 |  |
| Pruritus                                    |                    |                    |  |
| subjects affected / exposed                 | 24 / 206 (11.65%)  | 19 / 215 (8.84%)   |  |
| occurrences (all)                           | 34                 | 31                 |  |
| Nail toxicity                               |                    |                    |  |
| subjects affected / exposed                 | 24 / 206 (11.65%)  | 15 / 215 (6.98%)   |  |
| occurrences (all)                           | 27                 | 18                 |  |
| Erythema                                    |                    |                    |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 12 / 206 (5.83%)  | 16 / 215 (7.44%)  |  |
| occurrences (all)                               | 14                | 27                |  |
| Onycholysis                                     |                   |                   |  |
| subjects affected / exposed                     | 5 / 206 (2.43%)   | 16 / 215 (7.44%)  |  |
| occurrences (all)                               | 5                 | 17                |  |
| Renal and urinary disorders                     |                   |                   |  |
| Proteinuria                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 206 (0.49%)   | 22 / 215 (10.23%) |  |
| occurrences (all)                               | 2                 | 35                |  |
| Dysuria                                         |                   |                   |  |
| subjects affected / exposed                     | 7 / 206 (3.40%)   | 13 / 215 (6.05%)  |  |
| occurrences (all)                               | 8                 | 14                |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |
| Myalgia                                         |                   |                   |  |
| subjects affected / exposed                     | 60 / 206 (29.13%) | 59 / 215 (27.44%) |  |
| occurrences (all)                               | 115               | 137               |  |
| Musculoskeletal pain                            |                   |                   |  |
| subjects affected / exposed                     | 32 / 206 (15.53%) | 39 / 215 (18.14%) |  |
| occurrences (all)                               | 46                | 61                |  |
| Arthralgia                                      |                   |                   |  |
| subjects affected / exposed                     | 41 / 206 (19.90%) | 63 / 215 (29.30%) |  |
| occurrences (all)                               | 86                | 109               |  |
| Pain in extremity                               |                   |                   |  |
| subjects affected / exposed                     | 37 / 206 (17.96%) | 35 / 215 (16.28%) |  |
| occurrences (all)                               | 54                | 53                |  |
| Neck pain                                       |                   |                   |  |
| subjects affected / exposed                     | 10 / 206 (4.85%)  | 17 / 215 (7.91%)  |  |
| occurrences (all)                               | 13                | 17                |  |
| Back pain                                       |                   |                   |  |
| subjects affected / exposed                     | 26 / 206 (12.62%) | 32 / 215 (14.88%) |  |
| occurrences (all)                               | 37                | 39                |  |
| Bone pain                                       |                   |                   |  |
| subjects affected / exposed                     | 25 / 206 (12.14%) | 23 / 215 (10.70%) |  |
| occurrences (all)                               | 35                | 27                |  |
| Musculoskeletal chest pain                      |                   |                   |  |

|                                                                                       |                         |                         |  |
|---------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                      | 7 / 206 (3.40%)<br>8    | 14 / 215 (6.51%)<br>15  |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)                     | 8 / 206 (3.88%)<br>10   | 18 / 215 (8.37%)<br>33  |  |
| Infections and infestations                                                           |                         |                         |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 33 / 206 (16.02%)<br>58 | 27 / 215 (12.56%)<br>43 |  |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                          | 17 / 206 (8.25%)<br>21  | 19 / 215 (8.84%)<br>27  |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                          | 16 / 206 (7.77%)<br>22  | 17 / 215 (7.91%)<br>20  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 20 / 206 (9.71%)<br>25  | 18 / 215 (8.37%)<br>26  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 11 / 206 (5.34%)<br>15  | 21 / 215 (9.77%)<br>47  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 15 / 206 (7.28%)<br>18  | 9 / 215 (4.19%)<br>14   |  |
| Metabolism and nutrition disorders                                                    |                         |                         |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 25 / 206 (12.14%)<br>41 | 39 / 215 (18.14%)<br>58 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15 January 2007 | <ul style="list-style-type: none"><li>- Implemented central human epidermal growth factor receptor 2 (HER2) testing to ensure greater consistency in determination of HER2 status.</li><li>- Increased sample size to accommodate an assessment of PFS by an Independent Review Committee (not all participants could be assessed by such a procedure) for an intended US filing.</li><li>- Reversible posterior leukoencephalopathy syndrome (RPLS) was listed as an adverse event of special interest to ensure instances of this rare event were properly detected.</li><li>- Inclusion criterion for participants who had received adjuvant trastuzumab treatment was modified to better reflect the clinical reality after the earlier than expected approval of this treatment. The washout period for prior hormone treatment was also extended.</li><li>- The definition of inadequate liver function in the exclusion criteria was changed for better alignment with the labeling for docetaxel and the duration of subsequent trastuzumab administration was extended for greater compliance with the dosing recommendations at the time.</li><li>- Further clarifications and correction of typographical errors.</li></ul> |
| 06 March 2009   | <ul style="list-style-type: none"><li>- Monitoring of left ventricular ejection fraction (LVEF) was extended on the recommendation of the Data Safety Monitoring Board (DSMB).</li><li>- Exploratory interim analyses on PFS and OS were added on the request of the DSMB to enable an assessment of the risk/benefit ratio.</li><li>- Provision was made for participants randomized to the Trastuzumab+Docetaxel arm to receive bevacizumab after the end of the study if considered appropriate by DSMB on the basis of the interim analyses.</li><li>- Further clarifications were made and typographical errors were corrected.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported