



## Clinical trial results:

### A Randomized, 3 Arm, Multicenter, Phase III Study to Evaluate the Efficacy and the Safety of T-DM1 Combined With Pertuzumab or T-DM1 Combined With Pertuzumab-Placebo (Blinded for Pertuzumab), Versus the Combination of Trastuzumab Plus Taxane, as First Line Treatment in HER2 Positive Progressive or Recurrent Locally Advanced or Metastatic Breast Cancer (MBC)

#### Summary

|                          |                                        |
|--------------------------|----------------------------------------|
| EudraCT number           | 2009-017905-13                         |
| Trial protocol           | AT ES DE FR SE DK HU CZ GB IT BE PT GR |
| Global end of trial date | 16 September 2016                      |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v2 (current)    |
| This version publication date  | 30 August 2017  |
| First version publication date | 07 January 2017 |
| Version creation reason        |                 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | BO22589 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01120184 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                   |
|------------------------------|-----------------------------------------------------------------------------------|
| Sponsor organisation name    | Hoffmann-La Roche                                                                 |
| Sponsor organisation address | Grenzacherstrasse 124, CH, Basel, Switzerland, Switzerland, 4070                  |
| Public contact               | Medical Communications, Hoffmann-La Roche, +41 8008218590, genentech@druginfo.com |
| Scientific contact           | Medical Communications, Hoffmann-La Roche, +41 8008218590, genentech@druginfo.com |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 15 May 2016       |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 16 September 2016 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

This randomized, three-arm, multicenter, Phase III study was designed to evaluate the efficacy and safety of trastuzumab emtansine with and without pertuzumab, versus the combination of trastuzumab with taxane therapy, among subjects with human epidermal growth factor receptor 2 (HER2)-positive locally advanced breast cancer (LABC) or metastatic breast cancer (MBC) who had not received prior chemotherapy for their metastatic disease.

Protection of trial subjects:

All investigators were trained according to applicable Sponsor Standard Operating Procedures (SOPs). Roche and the investigators strictly adhered to the stated provisions in these guidelines. This was documented by the investigator's signature on the protocol agreeing to carry out all of its terms in accordance with the applicable regulations and law and to follow International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 29 June 2010     |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Efficacy, Safety |
| Long term follow-up duration                              | 67 Months        |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Germany: 41            |
| Country: Number of subjects enrolled | Korea, Republic of: 79 |
| Country: Number of subjects enrolled | Belgium: 20            |
| Country: Number of subjects enrolled | Bahamas: 6             |
| Country: Number of subjects enrolled | Portugal: 6            |
| Country: Number of subjects enrolled | Colombia: 5            |
| Country: Number of subjects enrolled | Panama: 5              |
| Country: Number of subjects enrolled | Switzerland: 4         |
| Country: Number of subjects enrolled | Greece: 2              |
| Country: Number of subjects enrolled | Turkey: 2              |
| Country: Number of subjects enrolled | Sweden: 2              |
| Country: Number of subjects enrolled | United States: 131     |

|                                      |                                                |
|--------------------------------------|------------------------------------------------|
| Country: Number of subjects enrolled | Brazil: 88                                     |
| Country: Number of subjects enrolled | Japan: 82                                      |
| Country: Number of subjects enrolled | United Kingdom: 74                             |
| Country: Number of subjects enrolled | France: 72                                     |
| Country: Number of subjects enrolled | Italy: 53                                      |
| Country: Number of subjects enrolled | Russian Federation: 50                         |
| Country: Number of subjects enrolled | Spain: 43                                      |
| Country: Number of subjects enrolled | Thailand: 39                                   |
| Country: Number of subjects enrolled | Poland: 31                                     |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 25                     |
| Country: Number of subjects enrolled | Canada: 23                                     |
| Country: Number of subjects enrolled | Philippines: 23                                |
| Country: Number of subjects enrolled | Macedonia, the former Yugoslav Republic of: 21 |
| Country: Number of subjects enrolled | Peru: 20                                       |
| Country: Number of subjects enrolled | Czech Republic: 19                             |
| Country: Number of subjects enrolled | Hungary: 19                                    |
| Country: Number of subjects enrolled | Australia: 18                                  |
| Country: Number of subjects enrolled | Taiwan: 17                                     |
| Country: Number of subjects enrolled | Mexico: 16                                     |
| Country: Number of subjects enrolled | Guatemala: 12                                  |
| Country: Number of subjects enrolled | Austria: 10                                    |
| Country: Number of subjects enrolled | Malaysia: 10                                   |
| Country: Number of subjects enrolled | New Zealand: 8                                 |
| Country: Number of subjects enrolled | Denmark: 7                                     |
| Country: Number of subjects enrolled | Romania: 6                                     |
| Country: Number of subjects enrolled | Argentina: 6                                   |
| Worldwide total number of subjects   | 1095                                           |
| EEA total number of subjects         | 405                                            |

Notes:

### Subjects enrolled per age group

|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 912 |
| From 65 to 84 years                       | 179 |
| 85 years and over                         | 4   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 1629 subjects were screened, of whom 1095 were randomized. There were 534 subjects who failed screening, most often due to non-centrally confirmed HER2 status or abnormal laboratory results.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Investigator, Subject          |

Blinding implementation details:

The study was considered open-label with respect to trastuzumab and trastuzumab emtansine treatment; however, subjects and investigators were blinded with respect to pertuzumab or placebo.

### Arms

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

Arm description:

Subjects received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m<sup>2</sup> IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m<sup>2</sup> IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

|                                        |                                                  |
|----------------------------------------|--------------------------------------------------|
| Arm type                               | Experimental                                     |
| Investigational medicinal product name | Trastuzumab                                      |
| Investigational medicinal product code |                                                  |
| Other name                             |                                                  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

Trastuzumab was administered via IV infusion and dosed depending upon the taxane selected. Subjects received either 8 mg/kg on Day 1 of Cycle 1 followed by 6 mg/kg on Day 1 of each subsequent 3-week cycle, or 4 mg/kg on Day 1 of Cycle 1 followed by 2 mg/kg weekly beginning on Day 8 of Cycle 1.

|                                        |                                                  |
|----------------------------------------|--------------------------------------------------|
| Investigational medicinal product name | Docetaxel                                        |
| Investigational medicinal product code |                                                  |
| Other name                             |                                                  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

Docetaxel was administered via IV infusion as 75 or 100 mg/m<sup>2</sup> on Day 1 of each 3-week cycle.

|                                        |                                                  |
|----------------------------------------|--------------------------------------------------|
| Investigational medicinal product name | Paclitaxel                                       |
| Investigational medicinal product code |                                                  |
| Other name                             |                                                  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

**Dosage and administration details:**

Paclitaxel was administered via IV infusion as 80 mg/m<sup>2</sup> weekly.

|                  |                                 |
|------------------|---------------------------------|
| <b>Arm title</b> | Trastuzumab Emtansine + Placebo |
|------------------|---------------------------------|

**Arm description:**

Subjects received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

|                                        |                                                  |
|----------------------------------------|--------------------------------------------------|
| Arm type                               | Experimental                                     |
| Investigational medicinal product name | Trastuzumab emtansine                            |
| Investigational medicinal product code |                                                  |
| Other name                             |                                                  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

**Dosage and administration details:**

Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion on Day 1 of each 3-week cycle.

|                                        |                                                  |
|----------------------------------------|--------------------------------------------------|
| Investigational medicinal product name | Placebo                                          |
| Investigational medicinal product code |                                                  |
| Other name                             |                                                  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

**Dosage and administration details:**

Subjects received the placebo equivalent to pertuzumab via IV infusion on Day 1 of each 3-week cycle.

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | Trastuzumab Emtansine + Pertuzumab |
|------------------|------------------------------------|

**Arm description:**

Subjects received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

|                                        |                                                  |
|----------------------------------------|--------------------------------------------------|
| Arm type                               | Experimental                                     |
| Investigational medicinal product name | Pertuzumab                                       |
| Investigational medicinal product code |                                                  |
| Other name                             |                                                  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

**Dosage and administration details:**

Pertuzumab was administered via IV infusion as 840 mg on Day 1 of Cycle 1, followed by 420 mg on Day 1 of each subsequent 3-week cycle.

|                                        |                                                  |
|----------------------------------------|--------------------------------------------------|
| Investigational medicinal product name | Trastuzumab emtansine                            |
| Investigational medicinal product code |                                                  |
| Other name                             |                                                  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

**Dosage and administration details:**

Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion on Day 1 of each 3-week cycle.

| Number of subjects in period 1            | Trastuzumab +<br>Taxane | Trastuzumab<br>Emtansine + Placebo | Trastuzumab<br>Emtansine +<br>Pertuzumab |
|-------------------------------------------|-------------------------|------------------------------------|------------------------------------------|
|                                           |                         |                                    |                                          |
| Started                                   | 365                     | 367                                | 363                                      |
| Treated                                   | 355                     | 365                                | 360                                      |
| Completed                                 | 0                       | 0                                  | 0                                        |
| Not completed                             | 365                     | 367                                | 363                                      |
| Physician decision                        | 9                       | 1                                  | 3                                        |
| Adverse event, non-fatal                  | -                       | 1                                  | -                                        |
| Death                                     | 170                     | 176                                | 169                                      |
| Sponsor Decision to Terminate<br>Study    | 133                     | 144                                | 143                                      |
| Subject/ Guardian Decision to<br>Withdraw | 32                      | 29                                 | 25                                       |
| Lost to follow-up                         | 13                      | 13                                 | 11                                       |
| Reason not Specified                      | 8                       | 3                                  | 12                                       |

## Baseline characteristics

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Trastuzumab + Taxane |
|-----------------------|----------------------|

Reporting group description:

Subjects received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m<sup>2</sup> IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m<sup>2</sup> IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Trastuzumab Emtansine + Placebo |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Trastuzumab Emtansine + Pertuzumab |
|-----------------------|------------------------------------|

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

| Reporting group values                             | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |
|----------------------------------------------------|----------------------|---------------------------------|------------------------------------|
| Number of subjects                                 | 365                  | 367                             | 363                                |
| Age categorical                                    |                      |                                 |                                    |
| Units: Subjects                                    |                      |                                 |                                    |
| In utero                                           | 0                    | 0                               | 0                                  |
| Preterm newborn infants (gestational age < 37 wks) | 0                    | 0                               | 0                                  |
| Newborns (0-27 days)                               | 0                    | 0                               | 0                                  |
| Infants and toddlers (28 days-23 months)           | 0                    | 0                               | 0                                  |
| Children (2-11 years)                              | 0                    | 0                               | 0                                  |
| Adolescents (12-17 years)                          | 0                    | 0                               | 0                                  |
| Adults (18-64 years)                               | 303                  | 306                             | 303                                |
| From 65-84 years                                   | 59                   | 61                              | 59                                 |
| 85 years and over                                  | 3                    | 0                               | 1                                  |
| Age Continuous                                     |                      |                                 |                                    |
| Units: years                                       |                      |                                 |                                    |
| arithmetic mean                                    | 54.2                 | 52.6                            | 52.2                               |
| standard deviation                                 | ± 11.3               | ± 11.4                          | ± 12                               |
| Gender, Male/Female                                |                      |                                 |                                    |
| Units: Subjects                                    |                      |                                 |                                    |
| Female                                             | 362                  | 365                             | 361                                |
| Male                                               | 3                    | 2                               | 2                                  |

|                        |       |  |  |
|------------------------|-------|--|--|
| Reporting group values | Total |  |  |
|------------------------|-------|--|--|

|                                                       |      |  |  |
|-------------------------------------------------------|------|--|--|
| Number of subjects                                    | 1095 |  |  |
| Age categorical                                       |      |  |  |
| Units: Subjects                                       |      |  |  |
| In utero                                              | 0    |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0    |  |  |
| Newborns (0-27 days)                                  | 0    |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0    |  |  |
| Children (2-11 years)                                 | 0    |  |  |
| Adolescents (12-17 years)                             | 0    |  |  |
| Adults (18-64 years)                                  | 912  |  |  |
| From 65-84 years                                      | 179  |  |  |
| 85 years and over                                     | 4    |  |  |
| Age Continuous                                        |      |  |  |
| Units: years                                          |      |  |  |
| arithmetic mean                                       |      |  |  |
| standard deviation                                    | -    |  |  |
| Gender, Male/Female                                   |      |  |  |
| Units: Subjects                                       |      |  |  |
| Female                                                | 1088 |  |  |
| Male                                                  | 7    |  |  |

## End points

### End points reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Trastuzumab + Taxane |
|-----------------------|----------------------|

Reporting group description:

Subjects received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m<sup>2</sup> IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m<sup>2</sup> IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Trastuzumab Emtansine + Placebo |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Trastuzumab Emtansine + Pertuzumab |
|-----------------------|------------------------------------|

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

|                            |                      |
|----------------------------|----------------------|
| Subject analysis set title | Trastuzumab + Taxane |
|----------------------------|----------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m<sup>2</sup> IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m<sup>2</sup> IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

|                            |                                 |
|----------------------------|---------------------------------|
| Subject analysis set title | Trastuzumab Emtansine + Placebo |
|----------------------------|---------------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

|                            |                                    |
|----------------------------|------------------------------------|
| Subject analysis set title | Trastuzumab Emtansine + Pertuzumab |
|----------------------------|------------------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

### Primary: Percentage of Subjects with Death or Disease Progression According to Independent Review Facility (IRF) Assessment

|                 |                                                                                                                                   |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Death or Disease Progression According to Independent Review Facility (IRF) Assessment <sup>[1]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|

End point description:

Tumor assessments were performed according to Response Evaluation Criteria in Solid Tumors (RECIST)

version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Disease progression was defined as a greater than or equal to ( $\geq$ ) 20 percent (%) and 5-millimeter (mm) increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of subjects with death or disease progression was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population (all subjects randomized in the study).

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

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics only

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 365                  | 367                             | 363                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 63.3                 | 64.3                            | 59.8                               |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Progression-Free Survival (PFS) According to IRF Assessment

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | Progression-Free Survival (PFS) According to IRF Assessment |
|-----------------|-------------------------------------------------------------|

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. PFS was defined as the time from randomization to first documented disease progression or death from any cause. Disease progression was defined as a  $\geq 20\%$  and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis, and corresponding confidence intervals (CIs) were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population (all subjects randomized in the study).

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

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values                 | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed      | 365                  | 367                             | 363                                |  |
| Units: months                    |                      |                                 |                                    |  |
| median (confidence interval 95%) | 13.7 (12.4 to 14.9)  | 14.1 (10.9 to 16.8)             | 15.2 (12.5 to 18.8)                |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                  | Statistical Analysis 1                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                           |                                                        |
| Direction of comparison: Trastuzumab Emtansine + Placebo versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent). |                                                        |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                           | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                     | 732                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                      | Pre-specified                                          |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                               |                                                        |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                     | = 0.3125 <sup>[2]</sup>                                |
| Method                                                                                                                                                                                                                                                                                                                                                                                                      | Logrank                                                |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                          | Hazard ratio (HR)                                      |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                              | 0.91                                                   |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                         |                                                        |
| level                                                                                                                                                                                                                                                                                                                                                                                                       | Other: 97.5 %                                          |
| sides                                                                                                                                                                                                                                                                                                                                                                                                       | 2-sided                                                |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                 | 0.73                                                   |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                 | 1.13                                                   |

Notes:

[2] - Test and p-value apply for superiority test. Two-sided significance level of 2.5% was used to adjust for independent comparison between each of the trastuzumab emtansine-containing arms and the trastuzumab + taxane arm.

| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                     | Statistical Analysis 2                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                              |                                                           |
| Direction of comparison: Trastuzumab Emtansine + Pertuzumab versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent). |                                                           |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                              | Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                        | 728                                                       |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                         | Pre-specified                                             |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                  |                                                           |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                        | = 0.1407 <sup>[3]</sup>                                   |
| Method                                                                                                                                                                                                                                                                                                                                                                                                         | Logrank                                                   |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                             | Hazard ratio (HR)                                         |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                 | 0.87                                                      |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                            |                                                           |
| level                                                                                                                                                                                                                                                                                                                                                                                                          | Other: 97.5 %                                             |
| sides                                                                                                                                                                                                                                                                                                                                                                                                          | 2-sided                                                   |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                    | 0.69                                                      |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                    | 1.08                                                      |

Notes:

[3] - Test and p-value apply for superiority test. Two-sided significance level of 2.5% was used to adjust for independent comparison between each of the trastuzumab emtansine-containing arms and the trastuzumab + taxane arm.

|                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                                         | Statistical Analysis 3                                               |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                                         |                                                                      |
| Direction of comparison: Trastuzumab Emtansine + Pertuzumab versus Trastuzumab Emtansine + Placebo. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent). |                                                                      |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                         | Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                   | 730                                                                  |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                    | Pre-specified                                                        |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                      |
| P-value                                                                                                                                                                                                                                                                                                                                                                                                                   | = 0.3075 <sup>[4]</sup>                                              |
| Method                                                                                                                                                                                                                                                                                                                                                                                                                    | Logrank                                                              |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                        | Hazard ratio (HR)                                                    |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                            | 0.91                                                                 |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                      |
| level                                                                                                                                                                                                                                                                                                                                                                                                                     | Other: 97.5 %                                                        |
| sides                                                                                                                                                                                                                                                                                                                                                                                                                     | 2-sided                                                              |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                               | 0.73                                                                 |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                               | 1.13                                                                 |

Notes:

[4] - Test and p-value apply for superiority test. Primary endpoint did not meet superiority of PFS for trastuzumab emtansine + pertuzumab versus trastuzumab + taxane (two-sided significance level 2.5%); thus, tests and p-value are considered descriptive.

### Secondary: Percentage of Subjects Who Died Prior to Clinical Cutoff

|                                                                                                                                                                                                                                                   |                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| End point title                                                                                                                                                                                                                                   | Percentage of Subjects Who Died Prior to Clinical Cutoff |
| End point description:                                                                                                                                                                                                                            |                                                          |
| The percentage of subjects who died prior to clinical cutoff was calculated as [number of subjects with event divided by the number analyzed multiplied by 100]. Analysis was performed on ITT population (all subjects randomized in the study). |                                                          |
| End point type                                                                                                                                                                                                                                    | Secondary                                                |
| End point timeframe:                                                                                                                                                                                                                              |                                                          |
| Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)                                                                                         |                                                          |

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 365                  | 367                             | 363                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 46.3                 | 47.7                            | 46.3                               |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS) at Clinical Cutoff

|                 |                                          |
|-----------------|------------------------------------------|
| End point title | Overall Survival (OS) at Clinical Cutoff |
|-----------------|------------------------------------------|

End point description:

OS was defined as the time from randomization to death from any cause. Median duration of OS was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Here, "9999" represents that the value is not applicable because Median duration of OS was not reached due to insufficient follow-up. Analysis was performed on ITT population.

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

End point timeframe:

Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

| End point values                 | Trastuzumab + Taxane   | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|------------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Reporting group        | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed      | 365                    | 367                             | 363                                |  |
| Units: months                    |                        |                                 |                                    |  |
| median (confidence interval 95%) | 50.86 (44.75 to 60.75) | 53.68 (48.36 to 64.36)          | 51.78 (47.87 to 9999)              |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                   |                                                           |
|-------------------|-----------------------------------------------------------|
| Comparison groups | Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab |
|-------------------|-----------------------------------------------------------|

|                                         |     |
|-----------------------------------------|-----|
| Number of subjects included in analysis | 728 |
|-----------------------------------------|-----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |  |
|---------------|--|
| Analysis type |  |
|---------------|--|

|                    |                   |
|--------------------|-------------------|
| Parameter estimate | Hazard ratio (HR) |
|--------------------|-------------------|

|                |      |
|----------------|------|
| Point estimate | 0.86 |
|----------------|------|

Confidence interval

|       |               |
|-------|---------------|
| level | Other: 97.5 % |
|-------|---------------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | 0.67 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 1.11 |
|-------------|------|

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

**Statistical analysis description:**

Direction of comparison: Trastuzumab Emtansine + Placebo versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis | 732                                                    |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| Parameter estimate                      | Hazard ratio (HR)                                      |
| Point estimate                          | 0.93                                                   |
| Confidence interval                     |                                                        |
| level                                   | Other: 97.5 %                                          |
| sides                                   | 2-sided                                                |
| lower limit                             | 0.73                                                   |
| upper limit                             | 1.2                                                    |

**Secondary: Percentage of Subjects with Death or Disease Progression According to Investigator Assessment**

|                 |                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Death or Disease Progression According to Investigator Assessment |
|-----------------|-----------------------------------------------------------------------------------------------|

**End point description:**

Tumor assessments were performed by the investigator according to RECIST version 1.1. Disease progression was defined as a  $\geq 20\%$  and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of subjects with death or disease progression was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population (all subjects randomized in the study).

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

**End point timeframe:**

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 365                  | 367                             | 363                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 72.1                 | 70.3                            | 67.5                               |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: PFS According to Investigator Assessment**

|                 |                                          |
|-----------------|------------------------------------------|
| End point title | PFS According to Investigator Assessment |
|-----------------|------------------------------------------|

**End point description:**

Tumor assessments were performed by the investigator according to RECIST version 1.1. PFS was defined as the time from randomization to first documented disease progression or death from any cause. Disease progression was defined as a  $\geq 20\%$  and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population (all subjects randomized in the study).

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

**End point timeframe:**

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values                 | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed      | 365                  | 367                             | 363                                |  |
| Units: months                    |                      |                                 |                                    |  |
| median (confidence interval 95%) | 12.5 (10.5 to 13.6)  | 14.1 (12.2 to 16.7)             | 14.8 (12.4 to 17.8)                |  |

**Statistical analyses**

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 1 |
|-----------------------------------|------------------------|

**Statistical analysis description:**

Direction of comparison: Trastuzumab Emtansine + Placebo versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis | 732                                                    |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| Parameter estimate                      | Hazard ratio (HR)                                      |
| Point estimate                          | 0.85                                                   |
| Confidence interval                     |                                                        |
| level                                   | Other: 97.5 %                                          |
| sides                                   | 2-sided                                                |
| lower limit                             | 0.69                                                   |
| upper limit                             | 1.04                                                   |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 2 |
|-----------------------------------|------------------------|

**Statistical analysis description:**

Direction of comparison: Trastuzumab Emtansine + Pertuzumab versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                                         |                                                           |
|-----------------------------------------|-----------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis | 728                                                       |
| Analysis specification                  | Pre-specified                                             |
| Analysis type                           |                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                         |
| Point estimate                          | 0.77                                                      |
| Confidence interval                     |                                                           |
| level                                   | Other: 97.5 %                                             |
| sides                                   | 2-sided                                                   |
| lower limit                             | 0.63                                                      |
| upper limit                             | 0.95                                                      |

### Secondary: Percentage of Subjects Experiencing Treatment Failure

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Percentage of Subjects Experiencing Treatment Failure |
| End point description:<br>Treatment failure was defined as the discontinuation of all study medications in the treatment arm for any reason including disease progression, treatment toxicity, death, physician decision, or subject withdrawal. The percentage of subjects with treatment failure was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population (all subjects randomized in the study). |                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Secondary                                             |
| End point timeframe:<br>Up to 48 months from randomization until clinical cutoff of 16-Sept-2014                                                                                                                                                                                                                                                                                                                                                                                        |                                                       |

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 365                  | 367                             | 363                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 85.8                 | 82.6                            | 80.2                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Treatment Failure (TTF)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Time to Treatment Failure (TTF) |
| End point description:<br>Treatment failure was defined as the discontinuation of all study medications in the treatment arm for any reason including disease progression, treatment toxicity, death, physician decision, or subject withdrawal. TTF was defined as the time from randomization to treatment failure. Median TTF was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population (all subjects randomized in the study). |                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Secondary                       |

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014

| End point values                 | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed      | 365                  | 367                             | 363                                |  |
| Units: months                    |                      |                                 |                                    |  |
| median (confidence interval 95%) | 10.2 (9.2 to 11.8)   | 12.1 (9.9 to 13.9)              | 11.8 (9.9 to 14.2)                 |  |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                                         |                                                           |
|-----------------------------------------|-----------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis | 728                                                       |
| Analysis specification                  | Pre-specified                                             |
| Analysis type                           |                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                         |
| Point estimate                          | 0.78                                                      |
| Confidence interval                     |                                                           |
| level                                   | Other: 97.5 %                                             |
| sides                                   | 2-sided                                                   |
| lower limit                             | 0.65                                                      |
| upper limit                             | 0.95                                                      |

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo versus Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                   |                                                        |
|-------------------|--------------------------------------------------------|
| Comparison groups | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
|-------------------|--------------------------------------------------------|

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 732               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           |                   |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.8               |
| Confidence interval                     |                   |
| level                                   | Other: 97.5 %     |
| sides                                   | 2-sided           |
| lower limit                             | 0.66              |
| upper limit                             | 0.97              |

### Secondary: One-Year Survival Rate

|                                                                                                                                                                                                                                                                                                                                          |                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| End point title                                                                                                                                                                                                                                                                                                                          | One-Year Survival Rate |
| End point description:<br>The percentage of subjects alive at 1 year after randomization was estimated as the one-year survival rate using Kaplan-Meier analysis, and corresponding CIs were computed using Greenwood's estimate of the standard error. Analysis was performed on ITT population (all subjects randomized in the study). |                        |
| End point type                                                                                                                                                                                                                                                                                                                           | Secondary              |
| End point timeframe:<br>From randomization until 1 year                                                                                                                                                                                                                                                                                  |                        |

| End point values                             | Trastuzumab + Taxane  | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------------------|-----------------------|---------------------------------|------------------------------------|--|
| Subject group type                           | Reporting group       | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed                  | 365                   | 367                             | 363                                |  |
| Units: percentage probability of being alive |                       |                                 |                                    |  |
| number (confidence interval 95%)             | 91.4 (88.44 to 94.41) | 92.4 (89.62 to 95.15)           | 91.9 (89 to 94.77)                 |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Grade ≥3 Adverse Events

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Percentage of Subjects with Grade ≥3 Adverse Events |
| End point description:<br>Adverse events were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activity of daily living with inability to perform bathing, dressing and undressing, feeding self, using the toilet, taking medications but not bedridden. Grade 4: An immediate threat to life. Urgent medical intervention is required in order to maintain survival. Grade 5: Death. Analysis was performed on safety population. |                                                     |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Secondary                                           |

End point timeframe:

Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (continuously until 28 days after last dose ]

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Subject analysis set | Subject analysis set            | Subject analysis set               |  |
| Number of subjects analysed   | 353                  | 361                             | 366                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 54.1                 | 45.4                            | 46.2                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Who Died at 2 Years

|                        |                                                                                  |
|------------------------|----------------------------------------------------------------------------------|
| End point title        | Percentage of Subjects Who Died at 2 Years                                       |
| End point description: | Analysis was performed on ITT population (all subjects randomized in the study). |
| End point type         | Secondary                                                                        |
| End point timeframe:   | From randomization until 2 years                                                 |

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 365                  | 367                             | 363                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 20.3                 | 20.2                            | 19.6                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival Truncated at 2 Years

|                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Overall Survival Truncated at 2 Years                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| End point description: | Overall Survival truncated at 2 years was defined as the time from the date of randomization to the date of death from any cause. Subjects who were alive at 2 years had been censored at 2 years. Overall survival truncated at 2 years was estimated using Kaplan-Meier analyses. Here, "9999" represents that data was not applicable because median was not reached at 2 years as most of the subjects were alive at that time point. Analysis was performed on ITT population. |

|                                  |           |
|----------------------------------|-----------|
| End point type                   | Secondary |
| End point timeframe:             |           |
| From randomization until 2 years |           |

| End point values                 | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed      | 365                  | 367                             | 363                                |  |
| Units: months                    |                      |                                 |                                    |  |
| median (confidence interval 95%) | 9999 (9999 to 9999)  | 9999 (9999 to 9999)             | 9999 (9999 to 9999)                |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Grade 5 Adverse Events

|                                                                                                                                                                         |                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| End point title                                                                                                                                                         | Percentage of Subjects with Grade 5 Adverse Events |
| End point description:                                                                                                                                                  |                                                    |
| Adverse events were graded according to NCI CTCAE version 4.0. Grade 5 adverse events are those events which led to death. Analysis was performed on safety population. |                                                    |
| End point type                                                                                                                                                          | Secondary                                          |
| End point timeframe:                                                                                                                                                    |                                                    |
| Up to 50 months from randomization until clinical cutoff of 16-Sept-2014 (continuously until 28 days after last dose)                                                   |                                                    |

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Subject analysis set | Subject analysis set            | Subject analysis set               |  |
| Number of subjects analysed   | 353                  | 361                             | 366                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 1.7                  | 1.1                             | 1.9                                |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Grade 3-4 Laboratory Parameters

|                                                                                                 |                                                             |
|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| End point title                                                                                 | Percentage of Subjects with Grade 3-4 Laboratory Parameters |
| End point description:                                                                          |                                                             |
| Laboratory results were graded according to NCI CTCAE version 4.0. Grade 3: Severe or medically |                                                             |

significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activity of daily living with inability to perform bathing, dressing and undressing, feeding self, using the toilet, taking medications but not bedridden. Grade 4: An immediate threat to life. Urgent medical intervention is required in order to maintain survival. Analysis was performed on ITT population (all subjects randomized in the study).

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

End point timeframe:

Day 1, 8, and 15 of Cycle 1–3 and on Day 1 of each subsequent cycle up to 50 months from randomization until clinical cutoff of 16-Sept-2014

| End point values                         | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|------------------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type                       | Subject analysis set | Subject analysis set            | Subject analysis set               |  |
| Number of subjects analysed              | 353                  | 361                             | 366                                |  |
| Units: percentage of subjects            |                      |                                 |                                    |  |
| number (not applicable)                  |                      |                                 |                                    |  |
| Hemoglobin-Low: Grade 3                  | 4.3                  | 5.8                             | 6.9                                |  |
| Neutrophils-Low: Grade 3                 | 20.2                 | 5.5                             | 5                                  |  |
| Neutrophils-Low: Grade 4                 | 43.8                 | 1.9                             | 0.8                                |  |
| Platelets-Low: Grade 3                   | 0.9                  | 12.7                            | 12.9                               |  |
| Platelets-Low: Grade 4                   | 0.3                  | 2.8                             | 2.5                                |  |
| Alkaline Phosphate-High: Grade 3         | 1.1                  | 3.9                             | 3                                  |  |
| Alanine Transaminase-High: Grade 3       | 3.4                  | 9.1                             | 8                                  |  |
| Alanine Transaminase-High: Grade 4       | 0                    | 0.3                             | 0.6                                |  |
| Aspartate Aminotransferase-High: Grade 3 | 1.1                  | 11.9                            | 6.9                                |  |
| Aspartate Aminotransferase-High: Grade 4 | 0                    | 0.3                             | 0.3                                |  |
| Creatinine-High: Grade 3                 | 0.9                  | 0.3                             | 1.1                                |  |
| Creatinine-High: Grade 4                 | 0                    | 0                               | 0.3                                |  |
| Potassium-Low: Grade 3                   | 4.3                  | 4.7                             | 5.2                                |  |
| Potassium-Low: Grade 4                   | 0.6                  | 1.7                             | 0.6                                |  |
| Total Bilirubin-High: Grade 3            | 0.3                  | 0.3                             | 0.3                                |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Decline of $\geq 2$ points from Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status

|                 |                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Decline of $\geq 2$ points from Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The ECOG performance status is a scale used to quantify cancer subjects' general well-being and activities of daily life. The scale ranges from 0 to 5, with 0 denoting perfect health and 5 indicating death. The 6 categories are 0=Asymptomatic (Fully active, able to carry on all predisease activities without restriction), 1=Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), 2=Symptomatic, < 50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work

activities. Up and about more than 50% of waking hours), 3=Symptomatic, > 50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours), 4=Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair), 5=Death. Analysis was performed on safety population.

|                                                                          |           |
|--------------------------------------------------------------------------|-----------|
| End point type                                                           | Secondary |
| End point timeframe:                                                     |           |
| Baseline, Day 1 of every Cycle up to Clinical Data Cut (up to 48 months) |           |

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Subject analysis set | Subject analysis set            | Subject analysis set               |  |
| Number of subjects analysed   | 353                  | 361                             | 366                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 7.6                  | 6.1                             | 7.9                                |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hospitalization Days

|                                                                                                                                                                                                                                                                                                                                                                 |                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                 | Hospitalization Days |
| End point description:                                                                                                                                                                                                                                                                                                                                          |                      |
| Hospitalization was defined as a non-administration-related hospitalization due to serious adverse event, while on study treatment. Reported values represent number of days admitted per subjects. Analysis was performed on safety population. Number of subjects analyzed=subjects with hospitalization and data available for calculation of the parameter. |                      |
| End point type                                                                                                                                                                                                                                                                                                                                                  | Secondary            |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                            |                      |
| Up to 48 months from randomization until clinical cutoff of 16-Sept-2014                                                                                                                                                                                                                                                                                        |                      |

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Subject analysis set | Subject analysis set            | Subject analysis set               |  |
| Number of subjects analysed   | 353                  | 361                             | 366                                |  |
| Units: days                   |                      |                                 |                                    |  |
| median (full range (min-max)) | 6 (1 to 50)          | 5 (1 to 117)                    | 8 (1 to 381)                       |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Hospitalization

|                                                                                                                                                                                                            |                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| End point title                                                                                                                                                                                            | Percentage of Subjects with Hospitalization |
| End point description:<br>Hospitalization was defined as a non-administration-related hospitalization due to serious adverse event, while on study treatment. Analysis was performed on safety population. |                                             |
| End point type                                                                                                                                                                                             | Secondary                                   |
| End point timeframe:<br>Up to 48 months from randomization until clinical cutoff of 16-Sept-2014                                                                                                           |                                             |

| End point values                 | Trastuzumab + Taxane  | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|-----------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Subject analysis set  | Subject analysis set            | Subject analysis set               |  |
| Number of subjects analysed      | 353                   | 361                             | 366                                |  |
| Units: percentage of subjects    |                       |                                 |                                    |  |
| number (confidence interval 95%) | 21.8 (17.62 to 26.36) | 20.2 (16.2 to 24.71)            | 22.1 (18.03 to 26.7)               |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Objective Response According to IRF Assessment

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Percentage of Subjects with Objective Response According to IRF Assessment |
| End point description:<br>Objective response was defined as having complete response (CR) or partial response (PR), assessed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a $\geq 30\%$ decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of subjects with a best overall response of CR or PR (ie, the objective response rate [ORR]) was calculated as [number of subjects meeting the respective criteria divided by the number analyzed] multiplied by 100. Corresponding CIs computed using the Blyth-Still-Casella exact method. Analysis performed on ITT population with measurable disease by IRF at Baseline. |                                                                            |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Secondary                                                                  |
| End point timeframe:<br>Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                            |

| End point values                 | Trastuzumab + Taxane  | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|-----------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Reporting group       | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed      | 287                   | 303                             | 299                                |  |
| Units: percentage of subjects    |                       |                                 |                                    |  |
| number (confidence interval 95%) | 67.9 (62.26 to 73.31) | 59.7 (54.07 to 65.3)            | 64.2 (58.62 to 69.65)              |  |

## Statistical analyses

|                                                                                      |                                                        |
|--------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                                    | Statistical Analysis 1                                 |
| Statistical analysis description:                                                    |                                                        |
| Direction of comparison: Trastuzumab Emtansine + Placebo versus Trastuzumab + Taxane |                                                        |
| Comparison groups                                                                    | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis                                              | 590                                                    |
| Analysis specification                                                               | Pre-specified                                          |
| Analysis type                                                                        |                                                        |
| Parameter estimate                                                                   | Difference in Response Rate                            |
| Point estimate                                                                       | -8.2                                                   |
| Confidence interval                                                                  |                                                        |
| level                                                                                | 95 %                                                   |
| sides                                                                                | 2-sided                                                |
| lower limit                                                                          | -15.9                                                  |
| upper limit                                                                          | -0.5                                                   |

|                                                                                    |                                                           |
|------------------------------------------------------------------------------------|-----------------------------------------------------------|
| <b>Statistical analysis title</b>                                                  | Statistical Analysis 2                                    |
| Statistical analysis description:                                                  |                                                           |
| Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane |                                                           |
| Comparison groups                                                                  | Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis                                            | 586                                                       |
| Analysis specification                                                             | Pre-specified                                             |
| Analysis type                                                                      |                                                           |
| Parameter estimate                                                                 | Difference in Response Rate                               |
| Point estimate                                                                     | -3.7                                                      |
| Confidence interval                                                                |                                                           |
| level                                                                              | 95 %                                                      |
| sides                                                                              | 2-sided                                                   |
| lower limit                                                                        | -11.4                                                     |
| upper limit                                                                        | 3.9                                                       |

|                                                                                               |                                                                      |
|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                             | Statistical Analysis 3                                               |
| Statistical analysis description:                                                             |                                                                      |
| Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo |                                                                      |
| Comparison groups                                                                             | Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Pertuzumab |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 602                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           |                             |
| Parameter estimate                      | Difference in Response Rate |
| Point estimate                          | 4.5                         |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -3.3                        |
| upper limit                             | 12.2                        |

## Secondary: Percentage of Subjects with Objective Response According to Investigator Assessment

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Objective Response According to Investigator Assessment |
|-----------------|-------------------------------------------------------------------------------------|

### End point description:

Objective response was defined as having CR or PR, assessed according to RECIST version 1.1, by investigator. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a  $\geq 30\%$  decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of subjects with a best overall response of CR or PR (ie, the ORR) was calculated as [number of subjects meeting the respective criteria divided by the number analyzed] multiplied by 100. Corresponding CIs were computed using the Blyth-Still-Casella exact method. Analysis was performed on ITT population (all subjects randomized in the study). Only subjects with measurable disease by investigator at Baseline were included.

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

### End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values                 | Trastuzumab + Taxane  | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|-----------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Reporting group       | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed      | 293                   | 314                             | 311                                |  |
| Units: percentage of subjects    |                       |                                 |                                    |  |
| number (confidence interval 95%) | 69.3 (63.74 to 74.52) | 64.6 (59.12 to 69.87)           | 67.5 (62.17 to 72.68)              |  |

## Statistical analyses

|                                   |                                                        |
|-----------------------------------|--------------------------------------------------------|
| Statistical analysis title        | Statistical Analysis 1                                 |
| Statistical analysis description: |                                                        |
| Direction of comparison:          | Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane |
| Comparison groups                 | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |

|                                         |                             |
|-----------------------------------------|-----------------------------|
| Number of subjects included in analysis | 607                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           |                             |
| Parameter estimate                      | Difference in Response Rate |
| Point estimate                          | -4.6                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -12.1                       |
| upper limit                             | 2.8                         |

|                                                                                    |                                                           |
|------------------------------------------------------------------------------------|-----------------------------------------------------------|
| <b>Statistical analysis title</b>                                                  | Statistical Analysis 2                                    |
| Statistical analysis description:                                                  |                                                           |
| Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane |                                                           |
| Comparison groups                                                                  | Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis                                            | 604                                                       |
| Analysis specification                                                             | Pre-specified                                             |
| Analysis type                                                                      |                                                           |
| Parameter estimate                                                                 | Difference in Response Rate                               |
| Point estimate                                                                     | -1.8                                                      |
| Confidence interval                                                                |                                                           |
| level                                                                              | 95 %                                                      |
| sides                                                                              | 2-sided                                                   |
| lower limit                                                                        | -9.2                                                      |
| upper limit                                                                        | 5.7                                                       |

|                                                                                               |                                                                      |
|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                             | Statistical Analysis 3                                               |
| Statistical analysis description:                                                             |                                                                      |
| Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo |                                                                      |
| Comparison groups                                                                             | Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis                                                       | 625                                                                  |
| Analysis specification                                                                        | Pre-specified                                                        |
| Analysis type                                                                                 |                                                                      |
| Parameter estimate                                                                            | Difference in Response Rate                                          |
| Point estimate                                                                                | 2.9                                                                  |
| Confidence interval                                                                           |                                                                      |
| level                                                                                         | 95 %                                                                 |
| sides                                                                                         | 2-sided                                                              |
| lower limit                                                                                   | -4.5                                                                 |
| upper limit                                                                                   | 10.3                                                                 |

---

## Secondary: Duration of Response According to IRF Assessment

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Duration of Response According to IRF Assessment |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                  |
| Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Duration of response was defined as the time from confirmed PR or CR to first documented disease progression or death from any cause. CR was defined as the disappearance of all target lesions and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a $\geq 30\%$ decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. Median duration of response was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on ITT population. Only subjects achieving CR or PR were included in the analysis. |                                                  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Secondary                                        |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                  |
| Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                  |

| End point values                 | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed      | 195                  | 181                             | 192                                |  |
| Units: months                    |                      |                                 |                                    |  |
| median (confidence interval 95%) | 12.5 (10.5 to 16.6)  | 20.7 (14.8 to 25)               | 21.2 (15.8 to 29.3)                |  |

## Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                        |                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                             | Statistical Analysis 1                                 |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                      |                                                        |
| Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent). |                                                        |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                      | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                | 376                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                 | Pre-specified                                          |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                          |                                                        |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                     | Hazard ratio (HR)                                      |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                         | 0.6                                                    |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                    |                                                        |
| level                                                                                                                                                                                                                                                                                                                                                                                                  | Other: 97.5 %                                          |
| sides                                                                                                                                                                                                                                                                                                                                                                                                  | 2-sided                                                |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                            | 0.43                                                   |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                            | 0.84                                                   |

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

**Statistical analysis description:**

Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                                         |                                                           |
|-----------------------------------------|-----------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis | 387                                                       |
| Analysis specification                  | Pre-specified                                             |
| Analysis type                           |                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                         |
| Point estimate                          | 0.62                                                      |
| Confidence interval                     |                                                           |
| level                                   | Other: 97.5 %                                             |
| sides                                   | 2-sided                                                   |
| lower limit                             | 0.45                                                      |
| upper limit                             | 0.85                                                      |

### Secondary: Percentage of Subjects with a Best Overall Response of CR, PR, or Stable Disease (SD) According to IRF Assessment

|                 |                                                                                                                   |
|-----------------|-------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with a Best Overall Response of CR, PR, or Stable Disease (SD) According to IRF Assessment |
|-----------------|-------------------------------------------------------------------------------------------------------------------|

**End point description:**

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a  $\geq 30\%$  decrease in sum of diameters of target lesions, taking as reference the Baseline sum. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient (20%) increase to qualify for disease progression. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of subjects with a best overall response of CR, PR, or SD was calculated as [number of subjects meeting the respective criteria divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population.

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

**End point timeframe:**

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 0 <sup>[5]</sup>     | 0 <sup>[6]</sup>                | 0 <sup>[7]</sup>                   |  |
| Units: percentage of subjects |                      |                                 |                                    |  |

**Notes:**

- [5] - This outcome was removed because it was redundant to another prespecified secondary endpoint.  
 [6] - This outcome was removed because it was redundant to another prespecified secondary endpoint.  
 [7] - This outcome was removed because it was redundant to another prespecified secondary endpoint.

**Statistical analyses**

## Secondary: Percentage of Subjects Experiencing a Clinically Significant Increase in Taxane-Related Treatment Symptoms as Measured by Taxane Subscale of the Functional Assessment of Cancer Therapy (FACT) Taxane (FACT-TaxS) Score

|                 |                                                                                                                                                                                                                          |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Experiencing a Clinically Significant Increase in Taxane-Related Treatment Symptoms as Measured by Taxane Subscale of the Functional Assessment of Cancer Therapy (FACT) Taxane (FACT-TaxS) Score |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### End point description:

The FACT-Taxane is a self-reported instrument which measures the health-related quality of life (HRQOL) of subjects receiving taxane-containing chemotherapy. The FACT-TaxS consists of 16 items including 11 neurotoxicity-related questions and 5 additional questions assessing arthralgia, myalgia, and skin discoloration. Items are rated from 0 (not at all) to 4 (very much) and a total score is inversely derived. Scores may range from 0 to 64, with higher scores indicating fewer/no symptoms. A minimally clinically important difference in treatment-related symptoms was defined as a  $\geq 5\%$  decrease (ie, 3.2 points) in FACT-TaxS score from Baseline. The percentage of subjects with treatment-related symptoms was calculated using following formula: [number of subjects meeting the above threshold divided by the number analyzed] multiplied by 100. Corresponding CIs computed using the Blyth-Still-Casella exact method. Analysis included randomized subjects who entered after Protocol Amendment C.

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

### End point timeframe:

Up to 39 months from randomization until clinical cutoff of 16-Sept-2014 (at Baseline, on Day 1 of Cycles 2 to 8 and every even-numbered cycle thereafter and/or up to 42 days after last dose)

| End point values                 | Trastuzumab + Taxane  | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|-----------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Reporting group       | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed      | 173                   | 171                             | 154                                |  |
| Units: percentage of subjects    |                       |                                 |                                    |  |
| number (confidence interval 95%) | 93.1 (88.48 to 96.06) | 60.8 (53.39 to 67.93)           | 68.8 (61.32 to 75.92)              |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

### Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis | 344                                                    |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| Parameter estimate                      | Difference in Symptom Rate                             |
| Point estimate                          | -32.2                                                  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -40     |
| upper limit         | -24     |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                                         |                                                           |
|-----------------------------------------|-----------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis | 327                                                       |
| Analysis specification                  | Pre-specified                                             |
| Analysis type                           |                                                           |
| Parameter estimate                      | Difference in Symptom Rate                                |
| Point estimate                          | -24.2                                                     |
| Confidence interval                     |                                                           |
| level                                   | 95 %                                                      |
| sides                                   | 2-sided                                                   |
| lower limit                             | -32                                                       |
| upper limit                             | -16                                                       |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab v Trastuzumab Emtansine + Placebo. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                                         |                                                                      |
|-----------------------------------------|----------------------------------------------------------------------|
| Comparison groups                       | Trastuzumab Emtansine + Placebo v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis | 325                                                                  |
| Analysis specification                  | Pre-specified                                                        |
| Analysis type                           |                                                                      |
| Parameter estimate                      | Difference in Symptom Rate                                           |
| Point estimate                          | 8                                                                    |
| Confidence interval                     |                                                                      |
| level                                   | 95 %                                                                 |
| sides                                   | 2-sided                                                              |
| lower limit                             | -2.3                                                                 |
| upper limit                             | 18.4                                                                 |

## Secondary: Percentage of Subjects Reporting Nausea According to the Relevant

## Single Items of The FACT Colorectal Cancel (FACT-C) Module

|                 |                                                                                                                              |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Nausea According to the Relevant Single Items of The FACT Colorectal Cancel (FACT-C) Module |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|

End point description:

The FACT-C is a self-reported instrument which measures HRQOL pertaining to colorectal cancer. Response options on each question may range from 0 (not at all) to 4 (very much). The percentage of subjects with nausea was calculated using following formula: [number of subjects with any level of either symptom divided by the number analyzed] multiplied by 100. Analyses were performed on the Protocol Amendment C Subpopulation. Only subjects with a FACTC score at the designated visit (n) were included in the analysis.

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

End point timeframe:

At Baseline, Day 8 of Cycle 1, and Days 1 and 8 of Cycle 2

| End point values                      | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|---------------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type                    | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed           | 173                  | 171                             | 154                                |  |
| Units: percentage of subjects         |                      |                                 |                                    |  |
| number (not applicable)               |                      |                                 |                                    |  |
| Nausea, Baseline (n=166,166,150)      | 22.3                 | 14.5                            | 21.3                               |  |
| Nausea, Cycle 1 Day 8 (n=121,114,95)  | 38                   | 36                              | 52.6                               |  |
| Nausea, Cycle 2 Day 1 (n=147,151,138) | 27.2                 | 20.5                            | 36.2                               |  |
| Nausea, Cycle 2 Day 8 (n=122,121,105) | 35.2                 | 28.1                            | 45.7                               |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Reporting Diarrhea According to the Relevant Single Items of The FACT-C Module

|                 |                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Reporting Diarrhea According to the Relevant Single Items of The FACT-C Module |
|-----------------|-------------------------------------------------------------------------------------------------------|

End point description:

The FACT-C is a self-reported instrument which measures HRQOL pertaining to colorectal cancer. Response options on each question may range from 0 (not at all) to 4 (very much). The percentage of subjects with diarrhea was calculated using following formula: [number of subjects with any level of either symptom divided by the number analyzed] multiplied by 100. Analyses were performed on the Protocol Amendment C Subpopulation. Only subjects with a FACTC score at the designated visit (n) were included in the analysis.

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

End point timeframe:

At Baseline, Day 8 of Cycle 1, and Days 1 and 8 of Cycle 2

| End point values                        | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-----------------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type                      | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed             | 173                  | 171                             | 154                                |  |
| Units: percentage of subjects           |                      |                                 |                                    |  |
| number (not applicable)                 |                      |                                 |                                    |  |
| Diarrhea, Baseline (n=173,170,153)      | 15                   | 7.6                             | 11.8                               |  |
| Diarrhea, Cycle 1 Day 8 (n=124,117,98)  | 34.7                 | 17.9                            | 34.7                               |  |
| Diarrhea, Cycle 2 Day 1 (n=161,160,144) | 24.2                 | 11.3                            | 39.6                               |  |
| Diarrhea, Cycle 2 Day 8 (n=125,123,107) | 34.4                 | 8.1                             | 41.1                               |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with a Clinically Significant Deterioration in Health Related Quality of Life (HRQoL) as measured by FACT Breast (FACT-B) Trial Outcome Index-Physical Function Breast (TOI-PFB) Score

|                 |                                                                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with a Clinically Significant Deterioration in Health Related Quality of Life (HRQoL) as measured by FACT Breast (FACT-B) Trial Outcome Index-Physical Function Breast (TOI-PFB) Score |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The FACT-B is a self-reported instrument which measures HRQOL of subjects with breast cancer. It consists of 5 subscales including physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and a breast cancer subscale (BCS). The TOI-PFB score is taken by adding the scores from the PWB (7 items), FWB (7 items), and BCS (9 items) subscales. Items are rated from 0 (not at all) to 4 (very much) and a total score is derived. Scores may range from 0 to 92, with higher scores indicating better HRQOL. A 5 point change has been identified as the clinically minimal important difference (CMID) on the FACT-TOI-PFB scale. The percentage of subjects with deterioration was calculated as [number of subjects meeting the above threshold divided by the number analyzed] multiplied by 100. Analysis was performed on the ITT population with baseline and at least one post baseline FACT-B TOI-PFB score.

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

End point timeframe:

Up to 39 months from randomization until clinical cutoff of 16-Sept-2014 (at Baseline, on Day 1 of Cycles 2 to 8 and every even-numbered cycle thereafter and/or up to 42 days after last dose)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 327                  | 352                             | 338                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 61.8                 | 50.9                            | 50.6                               |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Deterioration in HRQoL as Assessed by FACT-B TOI-PFB Score

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Time to Deterioration in HRQoL as Assessed by FACT-B TOI-PFB Score |
|-----------------|--------------------------------------------------------------------|

End point description:

The FACT-B is a self-reported instrument which measures HRQOL of subjects with breast cancer. It consists of 5 subscales including PWB, SWB, EWB, FWB, and BCS. The TOI-PFB score is taken by adding the scores from the PWB (7 items), FWB (7 items), and BCS (9 items) subscales. Items are rated from 0 (not at all) to 4 (very much) and a total score is derived. Scores may range from 0 to 92, with higher scores indicating better HRQOL. A 5 point change has been identified as the clinically minimal important difference (CMID) on the FACT-TOI-PFB scale. Time to deterioration was defined as the time from Baseline until the first decrease in FACT-B TOI-PFB score. Median time to deterioration was estimated using Kaplan-Meier analysis, and corresponding CIs were computed using the Brookmeyer-Crowley method. Analysis was performed on the ITT population with baseline and at least one post baseline FACT-B TOI-PFB score.

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

End point timeframe:

Baseline up to 39 months from randomization until clinical cutoff of 16-Sept-2014

| End point values                 | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type               | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed      | 327                  | 352                             | 338                                |  |
| Units: months                    |                      |                                 |                                    |  |
| median (confidence interval 95%) | 3.6 (3 to 4.4)       | 7.7 (6.2 to 11.9)               | 9 (5.1 to 14.5)                    |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Pertuzumab vs Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent).

|                                         |                                                           |
|-----------------------------------------|-----------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Pertuzumab |
| Number of subjects included in analysis | 665                                                       |
| Analysis specification                  | Pre-specified                                             |
| Analysis type                           |                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                         |
| Point estimate                          | 0.68                                                      |
| Confidence interval                     |                                                           |
| level                                   | 95 %                                                      |
| sides                                   | 2-sided                                                   |
| lower limit                             | 0.55                                                      |
| upper limit                             | 0.84                                                      |

|                                                                                                                                                                                                                                                                                                                                                                                                         |                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                       | Statistical Analysis 1                                 |
| Statistical analysis description:                                                                                                                                                                                                                                                                                                                                                                       |                                                        |
| Direction of comparison: Trastuzumab Emtansine + Placebo vs Trastuzumab + Taxane. Stratified Analysis: Stratification factors included world region (United States, Western Europe/Canada/Australia-Pacific, Eastern Europe, Asia, others); prior adjuvant/neoadjuvant therapy (no, yes [trastuzumab and/or lapatinib], yes [no trastuzumab and/or lapatinib]), and visceral disease (present, absent). |                                                        |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                 | 679                                                    |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                  | Pre-specified                                          |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                           |                                                        |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                      | Hazard ratio (HR)                                      |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                          | 0.7                                                    |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                     |                                                        |
| level                                                                                                                                                                                                                                                                                                                                                                                                   | 95 %                                                   |
| sides                                                                                                                                                                                                                                                                                                                                                                                                   | 2-sided                                                |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                             | 0.57                                                   |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                             | 0.86                                                   |

## Secondary: Change from Baseline in Rotterdam Symptom Checklist (RSCL) Activity Level Scale Score

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Change from Baseline in Rotterdam Symptom Checklist (RSCL) Activity Level Scale Score |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                       |
| The RSCL is a self-reported instrument which consists of 4 domains including physical symptom distress, psychological distress, activity level, and overall global life quality. Only the activity level scale was collected and assessed. Scores may range from 0 to 100, with higher scores indicating increased burden of disease. Mean RSCL activity scale score changes were calculated as [mean score at the assessment visit minus mean score at Baseline]. The higher the score, the higher the level of impairment or burden. Analysis was performed on ITT population. Only subjects with available data at baseline and Cycle 7 (Week 18) were included. |                                                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Secondary                                                                             |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                       |
| Baseline, Cycle 7 (Week 18)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                       |

| End point values                                | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type                              | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed                     | 365                  | 367                             | 363                                |  |
| Units: units on a scale                         |                      |                                 |                                    |  |
| arithmetic mean (confidence interval 95%)       |                      |                                 |                                    |  |
| Baseline (n=344,355,344)                        | 85 (82.9 to 87.2)    | 85.5 (83.3 to 87.8)             | 85.7 (83.5 to 87.8)                |  |
| Change From Baseline at Cycle 7 (n=261,252,261) | -1.6 (-4.2 to 1)     | 2.3 (0.4 to 4.2)                | -0.2 (-2.1 to 1.6)                 |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Work Productivity According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score

|                 |                                                                                                                             |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Work Productivity According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|

#### End point description:

The WPAI is a patient-reported measure which assesses the effect of general health and symptom severity on work productivity and regular activities. The General Health questionnaire asks subjects to estimate the number of hours missed from work due to reasons related and unrelated to their health problems, as well as the total number of hours actually worked in the preceding 7-day period. The percentage of subjects reporting that they were employed (working for pay) was assessed at baseline was assessed along with Absenteeism (work time missed), Presenteeism (impairment at work / reduced on-the-job effectiveness), Work productivity loss (overall work impairment / absenteeism plus presenteeism), and Activity Impairment. The reported changes represent change from baseline at Cycle 7. The score range for the scales of the WPAI is between 0 (no effect) to 100% (max effect). Analysis was performed on ITT population.

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

#### End point timeframe:

Baseline, Cycle 7 (Week 18)

| End point values                                   | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|----------------------------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type                                 | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed                        | 67                   | 64                              | 67                                 |  |
| Units: percent of work                             |                      |                                 |                                    |  |
| arithmetic mean (confidence interval 95%)          |                      |                                 |                                    |  |
| % Work Time Missed at Baseline (n=66,63,67)        | 15.3 (9.2 to 21.4)   | 9.5 (4.2 to 14.8)               | 13.6 (7.7 to 19.6)                 |  |
| Change in % Work Time Missed (n=35,33,36)          | 0.4 (-7.3 to 8.2)    | 0 (-4.5 to 4.5)                 | -4.3 (-13 to 4.6)                  |  |
| % Impairment While Working at Baseline(n=67,64,67) | 20 (14.1 to 25.9)    | 15.3 (9.5 to 21.1)              | 19.9 (13.6 to 26.1)                |  |
| Change in % Impairment While Working (n=34,32,35)  | 8.8 (2 to 15.6)      | -0.3 (-11 to 10.5)              | -2.7 (-11 to 5.2)                  |  |
| % Overall Work Impairment at Baseline (n=65,62,66) | 28.5 (20.7 to 36.2)  | 21.2 (13.8 to 28.7)             | 28.1 (20.3 to 35.9)                |  |
| Change in % Overall Work Impairment (n=34,31,35)   | 9.1 (-0.4 to 18.6)   | -1.1 (-13 to 11)                | -4.6 (-14 to 5)                    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Activity Impairment According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score

|                 |                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline in Activity Impairment According to Work Productivity and Activity Impairment (WPAI) Questionnaire Score |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|

End point description:

The WPAI is a patient-reported measure which assesses the effect of general health and symptom severity on work productivity and regular activities. The General Health questionnaire asks subjects to estimate the number of hours missed from work due to reasons related and unrelated to their health problems, as well as the total number of hours actually worked in the preceding 7-day period. The percentage of subjects reporting that they were employed (working for pay) was assessed at baseline was assessed along with Absenteeism (work time missed), Presenteeism (impairment at work / reduced on-the-job effectiveness), Work productivity loss (overall work impairment / absenteeism plus presenteeism), and Activity Impairment. The reported changes represent change from baseline at Cycle 7. The score range for the scales of the WPAI is between 0 (no effect) to 100% (max effect). Analysis was performed on ITT population.

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

End point timeframe:

Baseline, Cycle 7 (Week 18)

| End point values                                  | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|---------------------------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type                                | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed                       | 312                  | 334                             | 321                                |  |
| Units: units on a scale                           |                      |                                 |                                    |  |
| arithmetic mean (confidence interval 95%)         |                      |                                 |                                    |  |
| % Activity Impairment at Baseline (n=312,334,321) | 32.9 (29.6 to 36.3)  | 33.6 (30.2 to 37)               | 32.7 (29.5 to 36)                  |  |
| Change in % Activity Impairment (n=227,222,234)   | 4.5 (0.2 to 8.7)     | -5.3 (-9.5 to -1.1)             | -3.7 (-7.2 to -0.1)                |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with a Best Overall Response of CR or PR According to IRF Assessment Among Those with High Human Epidermal Growth Factor Receptor 2 (HER2) Messenger Ribonucleic Acid (mRNA) Levels

|                 |                                                                                                                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with a Best Overall Response of CR or PR According to IRF Assessment Among Those with High Human Epidermal Growth Factor Receptor 2 (HER2) Messenger Ribonucleic Acid (mRNA) Levels |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to <10 mm. PR was defined as a ≥30% decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined

using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of subjects with a best overall response of CR or PR (ie, the ORR) was calculated as [number of subjects meeting the respective criteria divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population with above the median HER2 mRNA expression (value greater than [ $>$ ] 59.71). Only subjects with measurable disease at Baseline were included in the analysis.

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

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 132                  | 136                             | 147                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 75                   | 66.9                            | 63.9                               |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis | 268                                                    |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| Parameter estimate                      | Odds ratio (OR)                                        |
| Point estimate                          | 0.67                                                   |
| Confidence interval                     |                                                        |
| level                                   | 95 %                                                   |
| sides                                   | 2-sided                                                |
| lower limit                             | 0.4                                                    |
| upper limit                             | 1.15                                                   |

## Secondary: Percentage of Subjects with a Best Overall Response of CR or PR According to IRF Assessment Among Those with Low HER2 mRNA Levels

|                 |                                                                                                                                   |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with a Best Overall Response of CR or PR According to IRF Assessment Among Those with Low HER2 mRNA Levels |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. CR was defined as the disappearance of all target and non-target lesions and short-axis reduction in pathological lymph nodes to  $<10$  mm. PR was defined as a  $\geq 30\%$  decrease in sum of diameters of target lesions, taking as reference the Baseline sum. Response was determined using 2 consecutive tumor assessments at least 4 weeks apart. The percentage of subjects with a best overall response of CR or PR (ie, the ORR) was calculated as [number of subjects meeting the respective criteria divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population

with below the median HER2 mRNA expression (value less than or equal to  $[\leq]$  59.71). Only subjects with measurable disease at Baseline were included in the analysis.

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

End point timeframe:

Up to 46 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 126                  | 147                             | 127                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 61.9                 | 51.7                            | 66.1                               |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo" vs Trastuzumab + Taxane

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis | 273                                                    |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| Parameter estimate                      | Odds ratio (OR)                                        |
| Point estimate                          | 0.66                                                   |
| Confidence interval                     |                                                        |
| level                                   | 95 %                                                   |
| sides                                   | 2-sided                                                |
| lower limit                             | 0.41                                                   |
| upper limit                             | 1.07                                                   |

## Secondary: Percentage of Subjects with Death or Disease Progression According to IRF Assessment Among Those with High HER2 mRNA Levels

|                 |                                                                                                                             |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Death or Disease Progression According to IRF Assessment Among Those with High HER2 mRNA Levels |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------|

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Disease progression was defined as a  $\geq 20\%$  and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of subjects with death or disease progression was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT Population (High HER2 mRNA Subpopulation).

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

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 160                  | 165                             | 173                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 59.4                 | 57.6                            | 56.1                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: PFS According to IRF Assessment Among Those with High HER2 mRNA Levels

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | PFS According to IRF Assessment Among Those with High HER2 mRNA Levels |
|-----------------|------------------------------------------------------------------------|

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. PFS was defined as the time from randomization to first documented disease progression or death from any cause. Disease progression was defined as a  $\geq 20\%$  and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis. Analysis was performed on ITT Population (High HER2 mRNA Subpopulation).

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

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 160                  | 165                             | 173                                |  |
| Units: months                 |                      |                                 |                                    |  |
| median (full range (min-max)) | 15.9 (0.1 to 46.4)   | 18.6 (0.1 to 46)                | 18.7 (0.1 to 48.1)                 |  |

### Statistical analyses

|                                                                                 |                                                        |
|---------------------------------------------------------------------------------|--------------------------------------------------------|
| <b>Statistical analysis title</b>                                               | Statistical Analysis 1                                 |
| Statistical analysis description:                                               |                                                        |
| Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane |                                                        |
| Comparison groups                                                               | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis                                         | 325                                                    |
| Analysis specification                                                          | Pre-specified                                          |
| Analysis type                                                                   |                                                        |
| Parameter estimate                                                              | Hazard ratio (HR)                                      |
| Point estimate                                                                  | 0.9                                                    |
| Confidence interval                                                             |                                                        |
| level                                                                           | Other: 97.5 %                                          |
| sides                                                                           | 2-sided                                                |
| lower limit                                                                     | 0.65                                                   |
| upper limit                                                                     | 1.25                                                   |

### Secondary: Percentage of Subjects with Death or Disease Progression According to IRF Assessment Among Those with Low HER2 mRNA Levels

|                 |                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects with Death or Disease Progression According to IRF Assessment Among Those with Low HER2 mRNA Levels |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. Disease progression was defined as a  $\geq 20\%$  and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). The percentage of subjects with death or disease progression was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT Population (Low HER2 mRNA Subpopulation).

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

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 170                  | 174                             | 157                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 66.5                 | 70.1                            | 62.4                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: PFS According to IRF Assessment Among Those with Low HER2 mRNA Levels

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | PFS According to IRF Assessment Among Those with Low HER2 mRNA Levels |
|-----------------|-----------------------------------------------------------------------|

End point description:

Tumor assessments were performed according to RECIST version 1.1, using radiographic images submitted to the IRF up to and including the confirmatory tumor assessment 4 to 6 weeks after study drug discontinuation. PFS was defined as the time from randomization to first documented disease progression or death from any cause. Disease progression was defined as a  $\geq 20\%$  and 5-mm increase in sum of diameters of target lesions, taking as reference the smallest sum obtained during the study, or appearance of new lesion(s). Median duration of PFS was estimated using Kaplan-Meier analysis. Analysis was performed on ITT Population (Low HER2 mRNA Subpopulation).

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

End point timeframe:

Up to 48 months from randomization until clinical cutoff of 16-Sept-2014 (at Screening, every 9 weeks for 81 weeks, then every 12 weeks thereafter and/or up to 42 days after last dose)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 170                  | 174                             | 157                                |  |
| Units: months                 |                      |                                 |                                    |  |
| median (full range (min-max)) | 12.4 (0.1 to 47.3)   | 10.2 (0.1 to 43.6)              | 14.5 (0.1 to 40.7)                 |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Direction of comparison: Trastuzumab Emtansine + Placebo v Trastuzumab + Taxane

|                                         |                                                        |
|-----------------------------------------|--------------------------------------------------------|
| Comparison groups                       | Trastuzumab + Taxane v Trastuzumab Emtansine + Placebo |
| Number of subjects included in analysis | 344                                                    |
| Analysis specification                  | Pre-specified                                          |
| Analysis type                           |                                                        |
| Parameter estimate                      | Hazard ratio (HR)                                      |
| Point estimate                          | 1                                                      |
| Confidence interval                     |                                                        |
| level                                   | Other: 97.5 %                                          |
| sides                                   | 2-sided                                                |
| lower limit                             | 0.74                                                   |
| upper limit                             | 1.34                                                   |

## Secondary: Percentage of Subjects Who Died Prior to Clinical Cutoff Among Those with High HER2 mRNA Levels

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Who Died Prior to Clinical Cutoff Among Those with High HER2 mRNA Levels |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

The percentage of subjects who died prior to clinical cutoff was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population

(High HER2 mRNA Subpopulation).

|                                                                                                                                                           |           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                                                            | Secondary |
| End point timeframe:                                                                                                                                      |           |
| Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination) |           |

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 160                  | 165                             | 173                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 38.8                 | 41.2                            | 45.1                               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: OS at Clinical Cutoff Among Those with High HER2 mRNA Levels

|                 |                                                              |
|-----------------|--------------------------------------------------------------|
| End point title | OS at Clinical Cutoff Among Those with High HER2 mRNA Levels |
|-----------------|--------------------------------------------------------------|

End point description:

OS was defined as the time from randomization to death from any cause. Median duration of OS was estimated using Kaplan-Meier analysis. Here, "9999" represents that the value is not applicable because Median duration of OS was not reached due to insufficient follow up. Analysis was performed on ITT population.

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

End point timeframe:

Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 160                  | 165                             | 173                                |  |
| Units: months                 |                      |                                 |                                    |  |
| median (full range (min-max)) | 9999 (50.86 to 9999) | 65.97 (54.54 to 67.98)          | 55.39 (45.23 to 9999)              |  |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Who Died Prior to Clinical Cutoff Among Those with Low HER2 mRNA Levels

|                 |                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Who Died Prior to Clinical Cutoff Among Those with Low HER2 mRNA Levels |
|-----------------|------------------------------------------------------------------------------------------------|

End point description:

The percentage of subjects who died prior to clinical cutoff was calculated as [number of subjects with event divided by the number analyzed] multiplied by 100. Analysis was performed on ITT population.

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

End point timeframe:

Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

| End point values              | Trastuzumab + Taxane | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|----------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group      | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 170                  | 174                             | 157                                |  |
| Units: percentage of subjects |                      |                                 |                                    |  |
| number (not applicable)       | 51.8                 | 52.9                            | 45.2                               |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: OS at Clinical Cutoff Among Those with Low HER2 mRNA Levels

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | OS at Clinical Cutoff Among Those with Low HER2 mRNA Levels |
|-----------------|-------------------------------------------------------------|

End point description:

OS was defined as the time from randomization to death from any cause. Median duration of OS was estimated using Kaplan-Meier analysis. Reported upper bound of confidence interval for "Trastuzumab Emtansine + Placebo" and confidence interval values for "Trastuzumab + Taxane" and "Trastuzumab Emtansine + Pertuzumab" are censored values. Here, "9999" represents that the value is not applicable because Median duration of OS was not reached due to insufficient follow up. Analysis was performed on ITT population.

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

End point timeframe:

Up to 70 months from randomization until clinical cutoff of 15-May-2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination)

| End point values              | Trastuzumab + Taxane   | Trastuzumab Emtansine + Placebo | Trastuzumab Emtansine + Pertuzumab |  |
|-------------------------------|------------------------|---------------------------------|------------------------------------|--|
| Subject group type            | Reporting group        | Reporting group                 | Reporting group                    |  |
| Number of subjects analysed   | 170                    | 174                             | 157                                |  |
| Units: months                 |                        |                                 |                                    |  |
| median (full range (min-max)) | 43.96 (37.19 to 54.87) | 47.84 (42.09 to 53.85)          | 53.29 (46.75 to 9999)              |  |

## **Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 70 months from randomization until clinical cutoff of 16 September 2016 (every 3 months until death, loss to follow-up, withdrawal, or study termination).

Adverse event reporting additional description:

Safety Population: All randomized subjects who received at least one dose of study treatment. Subjects were analyzed based on the treatment received.

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

### Dictionary used

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

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

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Trastuzumab Emtansine + Placebo |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab-placebo. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the placebo IV infusion, on Day 1 of each 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Trastuzumab + Taxane |
|-----------------------|----------------------|

Reporting group description:

Subjects received trastuzumab plus either docetaxel or paclitaxel. The regimen was chosen at the investigator's discretion. Option 1: trastuzumab 8 mg/kg via IV infusion on Day 1 of Cycle 1, then 6 mg/kg IV on Day 1 of each subsequent 3-week cycle; plus a minimum of 6 cycles with docetaxel 75 or 100 mg/m<sup>2</sup> IV on Day 1 of each 3-week cycle. Option 2: trastuzumab 4 mg/kg IV on Day 1 of Cycle 1, then 2 mg/kg IV weekly beginning on Day 8 of Cycle 1; plus a minimum of 18 weeks with paclitaxel 80 mg/m<sup>2</sup> IV weekly. Treatment continued until disease progression, unacceptable toxicity, or study termination. If trastuzumab or docetaxel were discontinued for toxicity, the other agent could be continued as monotherapy.

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Trastuzumab Emtansine + Pertuzumab |
|-----------------------|------------------------------------|

Reporting group description:

Subjects received trastuzumab emtansine plus pertuzumab. Trastuzumab emtansine was administered as 3.6 mg/kg via IV infusion, following completion of the pertuzumab IV infusion, on Day 1 of each 3-week cycle. Pertuzumab was given as 840 mg IV on Day 1 of Cycle 1, then 420 mg IV on Day 1 of each subsequent 3-week cycle. Treatment continued until disease progression, unacceptable toxicity, or study termination.

| Serious adverse events                                              | Trastuzumab Emtansine + Placebo | Trastuzumab + Taxane | Trastuzumab Emtansine + Pertuzumab |
|---------------------------------------------------------------------|---------------------------------|----------------------|------------------------------------|
| Total subjects affected by serious adverse events                   |                                 |                      |                                    |
| subjects affected / exposed                                         | 86 / 361 (23.82%)               | 81 / 353 (22.95%)    | 93 / 366 (25.41%)                  |
| number of deaths (all causes)                                       | 174                             | 170                  | 170                                |
| number of deaths resulting from adverse events                      |                                 |                      |                                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                 |                      |                                    |
| Acute leukaemia                                                     |                                 |                      |                                    |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Breast neoplasm                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic myeloid leukaemia                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colon neoplasm                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung adenocarcinoma                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myelodysplastic syndrome                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Squamous cell carcinoma of the cervix           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tumour haemorrhage                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Uterine leiomyoma                               |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Basal Cell Carcinoma                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intracranial Tumour Haemorrhage                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Hypertension                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematoma                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 361 (0.55%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhage                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Hypertensive crisis                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aneurysm                                        |                 |                 |                 |

|                                                      |                 |                 |                 |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypovolaemic Shock                                   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Orthostatic Hypotension                              |                 |                 |                 |
| subjects affected / exposed                          | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all      | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Pyrexia                                              |                 |                 |                 |
| subjects affected / exposed                          | 4 / 361 (1.11%) | 2 / 353 (0.57%) | 5 / 366 (1.37%) |
| occurrences causally related to treatment / all      | 3 / 5           | 0 / 2           | 2 / 6           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Fatigue                                              |                 |                 |                 |
| subjects affected / exposed                          | 1 / 361 (0.28%) | 3 / 353 (0.85%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all      | 0 / 1           | 2 / 3           | 1 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Non-cardiac chest pain                               |                 |                 |                 |
| subjects affected / exposed                          | 2 / 361 (0.55%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all      | 1 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Death                                                |                 |                 |                 |
| subjects affected / exposed                          | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           | 0 / 0           |
| General physical health deterioration                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 1           |
| Pain                                                 |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Asthenia                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Catheter site haematoma                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Malaise                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oedema                                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral swelling                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Adverse Drug Reaction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sudden Death                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Immune system disorders                         |                 |                 |                 |
| Hypersensitivity                                |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 361 (0.55%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 3 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anaphylactic reaction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 2 / 353 (0.57%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cytokine release syndrome                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anaphylactic Shock                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anaphylactoid Reaction                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Menorrhagia                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endometrial hypertrophy                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vaginal haemorrhage                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 3 / 353 (0.85%) | 3 / 366 (0.82%) |
| occurrences causally related to treatment / all | 0 / 1           | 2 / 3           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 2 / 361 (0.55%) | 4 / 353 (1.13%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 4           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           | 0 / 0           |
| Dyspnoea                                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 2 / 353 (0.57%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Epistaxis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 3 / 366 (0.82%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 2 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Interstitial lung disease                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           | 0 / 0           |
| Pneumothorax                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute respiratory failure                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Alveolitis allergic                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoxia                                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nasal turbinate hypertrophy                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary fibrosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Respiratory failure                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Acute Pulmonary Oedema                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depression                                      |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anxiety                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Suicide Attempt                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Mental Status Changes                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Product issues                                  |                 |                 |                 |
| Device Breakage                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Alanine aminotransferase increased              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aspartate aminotransferase increased            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Body temperature increased                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                  |
|-------------------------------------------------|-----------------|-----------------|------------------|
| International normalised ratio increased        |                 |                 |                  |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Oxygen saturation decreased                     |                 |                 |                  |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Injury, poisoning and procedural complications  |                 |                 |                  |
| Infusion related reaction                       |                 |                 |                  |
| subjects affected / exposed                     | 7 / 361 (1.94%) | 1 / 353 (0.28%) | 13 / 366 (3.55%) |
| occurrences causally related to treatment / all | 8 / 9           | 1 / 1           | 13 / 13          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Femur fracture                                  |                 |                 |                  |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 3 / 366 (0.82%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Pubis fracture                                  |                 |                 |                  |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 1 / 366 (0.27%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Arterial injury                                 |                 |                 |                  |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Contusion                                       |                 |                 |                  |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Fall                                            |                 |                 |                  |
| subjects affected / exposed                     | 2 / 361 (0.55%) | 0 / 353 (0.00%) | 0 / 366 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Femoral neck fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal stoma complication             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Radiation retinopathy                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal compression fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound secretion                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal Injury                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foot Fracture                                   |                 |                 |                 |

|                                                 |                                                                                                                                     |                 |                 |
|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 361 (0.00%)                                                                                                                     | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                               | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                               | 0 / 0           | 0 / 0           |
| Fracture                                        |                                                                                                                                     |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%)                                                                                                                     | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1                                                                                                                               | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                               | 0 / 0           | 0 / 0           |
| Stomal Hernia                                   |                                                                                                                                     |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%)                                                                                                                     | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                               | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                               | 0 / 0           | 0 / 0           |
| Uncoded serious adverse event                   | Additional description: Per investigator, this serious adverse event was, "gamma nail implant broke (status after femur fracture)." |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%)                                                                                                                     | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                               | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                               | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                                                                                                                                     |                 |                 |
| Atrial fibrillation                             |                                                                                                                                     |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%)                                                                                                                     | 1 / 353 (0.28%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                               | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                               | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                                                                                                                                     |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%)                                                                                                                     | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                               | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                               | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                                                                                                                                     |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%)                                                                                                                     | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                               | 0 / 0           | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                               | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                                                                                                                                     |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%)                                                                                                                     | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                                                                                                               | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                                                                                                                               | 1 / 1           | 0 / 0           |
| Pericardial effusion                            |                                                                                                                                     |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular tachycardia                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular tachycardia                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute Myocardial Infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Headache                                        |                 |                 |                 |
| subjects affected / exposed                     | 2 / 361 (0.55%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope                                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 361 (0.55%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Haemorrhage intracranial                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cognitive disorder                              |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depressed level of consciousness                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Guillain-Barre syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lacunar infarction                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Paraparesis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral sensory neuropathy                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Presyncope                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Somnolence                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular dementia                               |                 |                 |                 |

|                                                 |                 |                  |                 |
|-------------------------------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%)  | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Cerebral Haemorrhage                            |                 |                  |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%)  | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Epilepsy                                        |                 |                  |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%)  | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Neuropathy Peripheral                           |                 |                  |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%)  | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Sciatica                                        |                 |                  |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%)  | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Seizure                                         |                 |                  |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%)  | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                  |                 |
| Febrile neutropenia                             |                 |                  |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 13 / 353 (3.68%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 15 / 15          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Anaemia                                         |                 |                  |                 |
| subjects affected / exposed                     | 5 / 361 (1.39%) | 1 / 353 (0.28%)  | 6 / 366 (1.64%) |
| occurrences causally related to treatment / all | 3 / 6           | 0 / 1            | 3 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Neutropenia                                     |                 |                  |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 361 (0.00%) | 5 / 353 (1.42%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 5 / 5           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 361 (0.55%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypercoagulation                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Leukopenia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Vertigo                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Blindness transient                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Macular hole                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ocular hypertension                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 4 / 353 (1.13%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 6           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 4 / 366 (1.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 2 / 353 (0.57%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal haemorrhage                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anal fistula                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulum                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric haemorrhage                             |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric ulcer                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis erosive                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine perforation                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mallory-Weiss syndrome                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mouth haemorrhage                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nausea                                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Splenic artery aneurysm                         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Umbilical hernia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| Abdominal Discomfort                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ascites                                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal Haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhoidal Haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic Fibrosis                                |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic Haematoma                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Rash                                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 361 (0.55%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dermatomyositis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peau d'orange                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cutaneous Lupus Erythematosus                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Calculus urinary                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 6           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 361 (0.55%) | 1 / 353 (0.28%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bone pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 2 / 353 (0.57%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Exostosis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal chest pain                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal pain                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Neck pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pain in extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pathological fracture                           |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rotator cuff syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tenosynovitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 3 / 361 (0.83%) | 4 / 353 (1.13%) | 5 / 366 (1.37%) |
| occurrences causally related to treatment / all | 2 / 3           | 2 / 4           | 1 / 6           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           | 1 / 1           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 3 / 361 (0.83%) | 3 / 353 (0.85%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 1 / 4           | 1 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis                                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 4 / 366 (1.09%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Device related infection                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 2 / 366 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infection                                       |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Neutropenic sepsis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 3 / 353 (0.85%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 2 / 353 (0.57%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 2           | 0 / 0           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 3 / 366 (0.82%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Herpes zoster                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 2 / 353 (0.57%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 2 / 353 (0.57%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthritis infective                             |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atypical pneumonia                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Breast abscess                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chorioretinitis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Clostridium difficile colitis                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Clostridium difficile infection                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cystitis                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Empyema                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Erysipelas                                      |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Escherichia sepsis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis viral                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Influenza                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Klebsiella sepsis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Localised infection                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung infection                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mastitis                                        |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nasopharyngitis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia pneumococcal                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal abscess                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory tract infection                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Streptococcal sepsis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tooth infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abscess Limb                                    |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Appendicitis Perforated                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 361 (0.28%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Catheter Site Infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin Infection                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 361 (0.55%) | 0 / 353 (0.00%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Decreased appetite                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic ketoacidosis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypercalcaemia                                  |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hypokalaemia</b>                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hyponatraemia</b>                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 1 / 353 (0.28%) | 0 / 366 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Diabetes Mellitus</b>                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 361 (0.00%) | 0 / 353 (0.00%) | 1 / 366 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                           | Trastuzumab<br>Emtansine +<br>Placebo | Trastuzumab +<br>Taxane | Trastuzumab<br>Emtansine +<br>Pertuzumab |
|-------------------------------------------------------------|---------------------------------------|-------------------------|------------------------------------------|
| Total subjects affected by non-serious adverse events       |                                       |                         |                                          |
| subjects affected / exposed                                 | 352 / 361 (97.51%)                    | 342 / 353 (96.88%)      | 352 / 366 (96.17%)                       |
| <b>Vascular disorders</b>                                   |                                       |                         |                                          |
| Hypertension                                                |                                       |                         |                                          |
| subjects affected / exposed                                 | 37 / 361 (10.25%)                     | 19 / 353 (5.38%)        | 43 / 366 (11.75%)                        |
| occurrences (all)                                           | 87                                    | 27                      | 70                                       |
| Hot flush                                                   |                                       |                         |                                          |
| subjects affected / exposed                                 | 16 / 361 (4.43%)                      | 27 / 353 (7.65%)        | 12 / 366 (3.28%)                         |
| occurrences (all)                                           | 22                                    | 32                      | 19                                       |
| Lymphoedema                                                 |                                       |                         |                                          |
| subjects affected / exposed                                 | 7 / 361 (1.94%)                       | 27 / 353 (7.65%)        | 8 / 366 (2.19%)                          |
| occurrences (all)                                           | 8                                     | 35                      | 10                                       |
| <b>General disorders and administration site conditions</b> |                                       |                         |                                          |

|                                                 |                    |                    |                    |
|-------------------------------------------------|--------------------|--------------------|--------------------|
| Fatigue                                         |                    |                    |                    |
| subjects affected / exposed                     | 120 / 361 (33.24%) | 128 / 353 (36.26%) | 130 / 366 (35.52%) |
| occurrences (all)                               | 273                | 247                | 276                |
| Pyrexia                                         |                    |                    |                    |
| subjects affected / exposed                     | 96 / 361 (26.59%)  | 59 / 353 (16.71%)  | 118 / 366 (32.24%) |
| occurrences (all)                               | 156                | 85                 | 184                |
| Asthenia                                        |                    |                    |                    |
| subjects affected / exposed                     | 62 / 361 (17.17%)  | 57 / 353 (16.15%)  | 63 / 366 (17.21%)  |
| occurrences (all)                               | 205                | 163                | 211                |
| Chills                                          |                    |                    |                    |
| subjects affected / exposed                     | 55 / 361 (15.24%)  | 14 / 353 (3.97%)   | 97 / 366 (26.50%)  |
| occurrences (all)                               | 69                 | 15                 | 125                |
| Oedema peripheral                               |                    |                    |                    |
| subjects affected / exposed                     | 37 / 361 (10.25%)  | 98 / 353 (27.76%)  | 35 / 366 (9.56%)   |
| occurrences (all)                               | 56                 | 177                | 44                 |
| Mucosal inflammation                            |                    |                    |                    |
| subjects affected / exposed                     | 29 / 361 (8.03%)   | 40 / 353 (11.33%)  | 36 / 366 (9.84%)   |
| occurrences (all)                               | 46                 | 56                 | 54                 |
| Influenza like illness                          |                    |                    |                    |
| subjects affected / exposed                     | 31 / 361 (8.59%)   | 17 / 353 (4.82%)   | 32 / 366 (8.74%)   |
| occurrences (all)                               | 49                 | 33                 | 73                 |
| Non-cardiac chest pain                          |                    |                    |                    |
| subjects affected / exposed                     | 25 / 361 (6.93%)   | 24 / 353 (6.80%)   | 27 / 366 (7.38%)   |
| occurrences (all)                               | 36                 | 29                 | 35                 |
| Pain                                            |                    |                    |                    |
| subjects affected / exposed                     | 26 / 361 (7.20%)   | 29 / 353 (8.22%)   | 19 / 366 (5.19%)   |
| occurrences (all)                               | 29                 | 38                 | 24                 |
| Oedema                                          |                    |                    |                    |
| subjects affected / exposed                     | 11 / 361 (3.05%)   | 31 / 353 (8.78%)   | 3 / 366 (0.82%)    |
| occurrences (all)                               | 14                 | 51                 | 5                  |
| Reproductive system and breast disorders        |                    |                    |                    |
| Breast pain                                     |                    |                    |                    |
| subjects affected / exposed                     | 13 / 361 (3.60%)   | 18 / 353 (5.10%)   | 16 / 366 (4.37%)   |
| occurrences (all)                               | 13                 | 27                 | 19                 |
| Respiratory, thoracic and mediastinal disorders |                    |                    |                    |

|                                      |                    |                   |                    |
|--------------------------------------|--------------------|-------------------|--------------------|
| Epistaxis                            |                    |                   |                    |
| subjects affected / exposed          | 113 / 361 (31.30%) | 53 / 353 (15.01%) | 127 / 366 (34.70%) |
| occurrences (all)                    | 266                | 85                | 295                |
| Cough                                |                    |                   |                    |
| subjects affected / exposed          | 72 / 361 (19.94%)  | 74 / 353 (20.96%) | 79 / 366 (21.58%)  |
| occurrences (all)                    | 103                | 132               | 118                |
| Dyspnoea                             |                    |                   |                    |
| subjects affected / exposed          | 42 / 361 (11.63%)  | 56 / 353 (15.86%) | 53 / 366 (14.48%)  |
| occurrences (all)                    | 73                 | 89                | 74                 |
| Oropharyngeal pain                   |                    |                   |                    |
| subjects affected / exposed          | 31 / 361 (8.59%)   | 29 / 353 (8.22%)  | 30 / 366 (8.20%)   |
| occurrences (all)                    | 36                 | 36                | 41                 |
| Rhinorrhoea                          |                    |                   |                    |
| subjects affected / exposed          | 21 / 361 (5.82%)   | 26 / 353 (7.37%)  | 32 / 366 (8.74%)   |
| occurrences (all)                    | 26                 | 43                | 36                 |
| Psychiatric disorders                |                    |                   |                    |
| Insomnia                             |                    |                   |                    |
| subjects affected / exposed          | 51 / 361 (14.13%)  | 51 / 353 (14.45%) | 52 / 366 (14.21%)  |
| occurrences (all)                    | 77                 | 62                | 77                 |
| Anxiety                              |                    |                   |                    |
| subjects affected / exposed          | 26 / 361 (7.20%)   | 22 / 353 (6.23%)  | 33 / 366 (9.02%)   |
| occurrences (all)                    | 33                 | 42                | 41                 |
| Depression                           |                    |                   |                    |
| subjects affected / exposed          | 34 / 361 (9.42%)   | 17 / 353 (4.82%)  | 20 / 366 (5.46%)   |
| occurrences (all)                    | 42                 | 18                | 23                 |
| Investigations                       |                    |                   |                    |
| Aspartate aminotransferase increased |                    |                   |                    |
| subjects affected / exposed          | 54 / 361 (14.96%)  | 9 / 353 (2.55%)   | 28 / 366 (7.65%)   |
| occurrences (all)                    | 80                 | 11                | 56                 |
| Alanine aminotranseferase increased  |                    |                   |                    |
| subjects affected / exposed          | 41 / 361 (11.36%)  | 10 / 353 (2.83%)  | 35 / 366 (9.56%)   |
| occurrences (all)                    | 67                 | 12                | 57                 |
| Weight decreased                     |                    |                   |                    |
| subjects affected / exposed          | 24 / 361 (6.65%)   | 7 / 353 (1.98%)   | 30 / 366 (8.20%)   |
| occurrences (all)                    | 44                 | 10                | 41                 |
| Ejection fraction decreased          |                    |                   |                    |

|                                                                                              |                           |                          |                           |
|----------------------------------------------------------------------------------------------|---------------------------|--------------------------|---------------------------|
| subjects affected / exposed<br>occurrences (all)                                             | 7 / 361 (1.94%)<br>8      | 31 / 353 (8.78%)<br>36   | 16 / 366 (4.37%)<br>18    |
| Gamma- glutamyltranseferase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 30 / 361 (8.31%)<br>38    | 1 / 353 (0.28%)<br>1     | 17 / 366 (4.64%)<br>23    |
| Nervous system disorders                                                                     |                           |                          |                           |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                 | 116 / 361 (32.13%)<br>281 | 80 / 353 (22.66%)<br>165 | 120 / 366 (32.79%)<br>261 |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)                    | 52 / 361 (14.40%)<br>84   | 99 / 353 (28.05%)<br>171 | 69 / 366 (18.85%)<br>129  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)            | 47 / 361 (13.02%)<br>69   | 70 / 353 (19.83%)<br>125 | 46 / 366 (12.57%)<br>74   |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                | 30 / 361 (8.31%)<br>44    | 54 / 353 (15.30%)<br>67  | 50 / 366 (13.66%)<br>81   |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                             | 31 / 361 (8.59%)<br>51    | 41 / 353 (11.61%)<br>57  | 43 / 366 (11.75%)<br>74   |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                | 38 / 361 (10.53%)<br>67   | 35 / 353 (9.92%)<br>48   | 38 / 366 (10.38%)<br>77   |
| Blood and lymphatic system disorders                                                         |                           |                          |                           |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                              | 44 / 361 (12.19%)<br>186  | 74 / 353 (20.96%)<br>174 | 37 / 366 (10.11%)<br>152  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                                  | 48 / 361 (13.30%)<br>74   | 39 / 353 (11.05%)<br>61  | 59 / 366 (16.12%)<br>142  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                         | 52 / 361 (14.40%)<br>145  | 0 / 353 (0.00%)<br>0     | 61 / 366 (16.67%)<br>185  |
| Ear and labyrinth disorders                                                                  |                           |                          |                           |

|                                                                                                                  |                           |                           |                           |
|------------------------------------------------------------------------------------------------------------------|---------------------------|---------------------------|---------------------------|
| Vertigo<br>subjects affected / exposed<br>occurrences (all)                                                      | 17 / 361 (4.71%)<br>33    | 11 / 353 (3.12%)<br>15    | 21 / 366 (5.74%)<br>28    |
| Eye disorders                                                                                                    |                           |                           |                           |
| Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)                                        | 13 / 361 (3.60%)<br>19    | 48 / 353 (13.60%)<br>58   | 19 / 366 (5.19%)<br>22    |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)                                                      | 25 / 361 (6.93%)<br>26    | 13 / 353 (3.68%)<br>14    | 24 / 366 (6.56%)<br>28    |
| Vision Blurred<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences (all) | 13 / 361 (3.60%)<br>15    | 10 / 353 (2.83%)<br>15    | 19 / 366 (5.19%)<br>24    |
| Gastrointestinal disorders                                                                                       |                           |                           |                           |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                       | 174 / 361 (48.20%)<br>526 | 131 / 353 (37.11%)<br>308 | 192 / 366 (52.46%)<br>633 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                                    | 92 / 361 (25.48%)<br>151  | 173 / 353 (49.01%)<br>466 | 178 / 366 (48.63%)<br>550 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                     | 80 / 361 (22.16%)<br>136  | 69 / 353 (19.55%)<br>146  | 111 / 366 (30.33%)<br>215 |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                                 | 82 / 361 (22.71%)<br>150  | 72 / 353 (20.40%)<br>119  | 71 / 366 (19.40%)<br>138  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                                   | 37 / 361 (10.25%)<br>51   | 57 / 353 (16.15%)<br>76   | 42 / 366 (11.48%)<br>65   |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                                                    | 33 / 361 (9.14%)<br>55    | 38 / 353 (10.76%)<br>48   | 48 / 366 (13.11%)<br>94   |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                                         | 39 / 361 (10.80%)<br>62   | 31 / 353 (8.78%)<br>53    | 46 / 366 (12.57%)<br>70   |

|                                                                          |                          |                           |                          |
|--------------------------------------------------------------------------|--------------------------|---------------------------|--------------------------|
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)            | 52 / 361 (14.40%)<br>74  | 13 / 353 (3.68%)<br>21    | 45 / 366 (12.30%)<br>55  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 35 / 361 (9.70%)<br>51   | 31 / 353 (8.78%)<br>44    | 41 / 366 (11.20%)<br>70  |
| Gingival bleeding<br>subjects affected / exposed<br>occurrences (all)    | 31 / 361 (8.59%)<br>50   | 4 / 353 (1.13%)<br>5      | 25 / 366 (6.83%)<br>44   |
| Haemorrhoids<br>subjects affected / exposed<br>occurrences (all)         | 12 / 361 (3.32%)<br>20   | 9 / 353 (2.55%)<br>9      | 22 / 366 (6.01%)<br>44   |
| Skin and subcutaneous tissue disorders                                   |                          |                           |                          |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)             | 26 / 361 (7.20%)<br>28   | 212 / 353 (60.06%)<br>250 | 33 / 366 (9.02%)<br>34   |
| Rash<br>subjects affected / exposed<br>occurrences (all)                 | 62 / 361 (17.17%)<br>109 | 86 / 353 (24.36%)<br>150  | 89 / 366 (24.32%)<br>139 |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)             | 28 / 361 (7.76%)<br>46   | 32 / 353 (9.07%)<br>40    | 51 / 366 (13.93%)<br>85  |
| Nail disorder<br>subjects affected / exposed<br>occurrences (all)        | 11 / 361 (3.05%)<br>12   | 39 / 353 (11.05%)<br>45   | 19 / 366 (5.19%)<br>20   |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)             | 24 / 361 (6.65%)<br>26   | 24 / 353 (6.80%)<br>30    | 29 / 366 (7.92%)<br>41   |
| Erythema<br>subjects affected / exposed<br>occurrences (all)             | 13 / 361 (3.60%)<br>14   | 24 / 353 (6.80%)<br>37    | 20 / 366 (5.46%)<br>27   |
| Dermatitis acneiform<br>subjects affected / exposed<br>occurrences (all) | 16 / 361 (4.43%)<br>16   | 6 / 353 (1.70%)<br>6      | 27 / 366 (7.38%)<br>41   |
| Palmar-plantar erythrodysaesthesia<br>syndrome                           |                          |                           |                          |

|                                                 |                   |                   |                   |
|-------------------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 6 / 361 (1.66%)   | 26 / 353 (7.37%)  | 11 / 366 (3.01%)  |
| occurrences (all)                               | 7                 | 29                | 14                |
| Nail discolouration                             |                   |                   |                   |
| subjects affected / exposed                     | 5 / 361 (1.39%)   | 25 / 353 (7.08%)  | 1 / 366 (0.27%)   |
| occurrences (all)                               | 5                 | 25                | 1                 |
| Onychoclasia                                    |                   |                   |                   |
| subjects affected / exposed                     | 19 / 361 (5.26%)  | 13 / 353 (3.68%)  | 17 / 366 (4.64%)  |
| occurrences (all)                               | 24                | 16                | 20                |
| Musculoskeletal and connective tissue disorders |                   |                   |                   |
| Arthralgia                                      |                   |                   |                   |
| subjects affected / exposed                     | 83 / 361 (22.99%) | 91 / 353 (25.78%) | 71 / 366 (19.40%) |
| occurrences (all)                               | 138               | 145               | 103               |
| Myalgia                                         |                   |                   |                   |
| subjects affected / exposed                     | 66 / 361 (18.28%) | 82 / 353 (23.23%) | 61 / 366 (16.67%) |
| occurrences (all)                               | 152               | 163               | 117               |
| Back pain                                       |                   |                   |                   |
| subjects affected / exposed                     | 60 / 361 (16.62%) | 46 / 353 (13.03%) | 63 / 366 (17.21%) |
| occurrences (all)                               | 77                | 65                | 87                |
| Pain in extremity                               |                   |                   |                   |
| subjects affected / exposed                     | 53 / 361 (14.68%) | 48 / 353 (13.60%) | 54 / 366 (14.75%) |
| occurrences (all)                               | 82                | 67                | 77                |
| Muscle spasms                                   |                   |                   |                   |
| subjects affected / exposed                     | 32 / 361 (8.86%)  | 15 / 353 (4.25%)  | 62 / 366 (16.94%) |
| occurrences (all)                               | 42                | 20                | 106               |
| Musculoskeletal pain                            |                   |                   |                   |
| subjects affected / exposed                     | 30 / 361 (8.31%)  | 23 / 353 (6.52%)  | 37 / 366 (10.11%) |
| occurrences (all)                               | 38                | 29                | 50                |
| Bone pain                                       |                   |                   |                   |
| subjects affected / exposed                     | 17 / 361 (4.71%)  | 33 / 353 (9.35%)  | 29 / 366 (7.92%)  |
| occurrences (all)                               | 21                | 51                | 69                |
| Musculoskeletal chest pain                      |                   |                   |                   |
| subjects affected / exposed                     | 13 / 361 (3.60%)  | 17 / 353 (4.82%)  | 20 / 366 (5.46%)  |
| occurrences (all)                               | 16                | 21                | 21                |
| Neck Pain                                       |                   |                   |                   |

|                                                  |                        |                        |                        |
|--------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all) | 12 / 361 (3.32%)<br>13 | 12 / 353 (3.40%)<br>13 | 24 / 366 (6.56%)<br>31 |
| Infections and infestations                      |                        |                        |                        |
| Upper respiratory tract infection                |                        |                        |                        |
| subjects affected / exposed                      | 50 / 361 (13.85%)      | 55 / 353 (15.58%)      | 66 / 366 (18.03%)      |
| occurrences (all)                                | 85                     | 104                    | 147                    |
| Nasopharyngitis                                  |                        |                        |                        |
| subjects affected / exposed                      | 52 / 361 (14.40%)      | 49 / 353 (13.88%)      | 66 / 366 (18.03%)      |
| occurrences (all)                                | 87                     | 100                    | 147                    |
| Urinary tract infection                          |                        |                        |                        |
| subjects affected / exposed                      | 31 / 361 (8.59%)       | 29 / 353 (8.22%)       | 41 / 366 (11.20%)      |
| occurrences (all)                                | 55                     | 43                     | 72                     |
| Rhinitis                                         |                        |                        |                        |
| subjects affected / exposed                      | 25 / 361 (6.93%)       | 18 / 353 (5.10%)       | 24 / 366 (6.56%)       |
| occurrences (all)                                | 29                     | 23                     | 32                     |
| Influenza                                        |                        |                        |                        |
| subjects affected / exposed                      | 22 / 361 (6.09%)       | 14 / 353 (3.97%)       | 25 / 366 (6.83%)       |
| occurrences (all)                                | 24                     | 19                     | 36                     |
| Paronychia                                       |                        |                        |                        |
| subjects affected / exposed                      | 8 / 361 (2.22%)        | 22 / 353 (6.23%)       | 30 / 366 (8.20%)       |
| occurrences (all)                                | 11                     | 31                     | 56                     |
| Pharyngitis                                      |                        |                        |                        |
| subjects affected / exposed                      | 19 / 361 (5.26%)       | 14 / 353 (3.97%)       | 17 / 366 (4.64%)       |
| occurrences (all)                                | 21                     | 14                     | 18                     |
| Conjunctivitis                                   |                        |                        |                        |
| subjects affected / exposed                      | 14 / 361 (3.88%)       | 21 / 353 (5.95%)       | 17 / 366 (4.64%)       |
| occurrences (all)                                | 18                     | 25                     | 20                     |
| Bronchitis                                       |                        |                        |                        |
| alternative assessment type:<br>Systematic       |                        |                        |                        |
| subjects affected / exposed                      | 9 / 361 (2.49%)        | 14 / 353 (3.97%)       | 20 / 366 (5.46%)       |
| occurrences (all)                                | 9                      | 15                     | 22                     |
| Metabolism and nutrition disorders               |                        |                        |                        |
| Decreased appetite                               |                        |                        |                        |
| subjects affected / exposed                      | 84 / 361 (23.27%)      | 76 / 353 (21.53%)      | 84 / 366 (22.95%)      |
| occurrences (all)                                | 164                    | 129                    | 156                    |
| Hypokalaemia                                     |                        |                        |                        |

|                             |                  |                  |                  |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 19 / 361 (5.26%) | 15 / 353 (4.25%) | 30 / 366 (8.20%) |
| occurrences (all)           | 23               | 18               | 40               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 07 March 2011    | Updates to the protocol included truncation of OS at 2 years as a secondary endpoint, addition of several quality of life assessments including FACT instruments, changes in the assessment schedule, clarification of the study population and eligibility criteria, and addition of treatment guidelines for cases of study drug discontinuation.                                                                                                                                          |
| 11 October 2011  | The protocol was amended to remove an interim futility analysis and to specify the new nonproprietary name 'trastuzumab emtansine' (formerly T-DM1).                                                                                                                                                                                                                                                                                                                                         |
| 29 May 2013      | The protocol was revised in order to allow for formal comparison of both trastuzumab emtansine arms, specify statistical assumptions, evaluate OS within high and low HER2 mRNA subsets, remove the clinical benefit rate (CR/PR/SD) as a redundant secondary endpoint, clarify committee procedures, further update the schedule of assessments, and add the option for subjects to cross over to the best treatment arm if OS was more favorable in one of the trastuzumab emtansine arms. |
| 01 November 2013 | The protocol was modified to add safety guidance on hepatotoxicity, including updated language for hemorrhage and Hy's Law.                                                                                                                                                                                                                                                                                                                                                                  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported