



## Clinical trial results:

**A Phase III trial to compare the safety and efficacy of lapatinib plus trastuzumab plus an aromatase inhibitor (AI) vs. trastuzumab plus an AI vs. lapatinib plus an AI as 1st- or 2nd- line therapy in postmenopausal subjects with hormone receptor+, HER2-positive metastatic breast cancer (MBC) who received prior trastuzumab and endocrine therapies**

### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2010-019577-16                         |
| Trial protocol           | DE HU IE PL BE BG NO GB LT PT ES GR IT |
| Global end of trial date | 06 June 2022                           |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v2 (current)  |
| This version publication date  | 23 March 2025 |
| First version publication date | 05 May 2023   |
| Version creation reason        |               |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 114299 |
|-----------------------|--------|

#### Additional study identifiers

|                                    |  |
|------------------------------------|--|
| ISRCTN number                      | -  |
| ClinicalTrials.gov id (NCT number) | NCT01160211  |
| WHO universal trial number (UTN)   | -  |
| Other trial identifiers            | Novartis: CLAP016A2307, GlaxoSmithKline: EGF114299 |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland,  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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                       | 06 June 2022 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 06 June 2022 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to demonstrate superiority of Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) combination (treatment group A) vs. Trastuzumab + Aromatase Inhibitor (AI) combination (treatment group B) for Progression Free Survival (PFS).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 05 May 2011 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 27          |
| Country: Number of subjects enrolled | Australia: 2           |
| Country: Number of subjects enrolled | Belgium: 2             |
| Country: Number of subjects enrolled | Brazil: 50             |
| Country: Number of subjects enrolled | Bulgaria: 23           |
| Country: Number of subjects enrolled | China: 13              |
| Country: Number of subjects enrolled | Croatia: 2             |
| Country: Number of subjects enrolled | France: 5              |
| Country: Number of subjects enrolled | Germany: 5             |
| Country: Number of subjects enrolled | United Kingdom: 4      |
| Country: Number of subjects enrolled | Greece: 10             |
| Country: Number of subjects enrolled | Hong Kong: 7           |
| Country: Number of subjects enrolled | Hungary: 17            |
| Country: Number of subjects enrolled | India: 2               |
| Country: Number of subjects enrolled | Israel: 4              |
| Country: Number of subjects enrolled | Italy: 1               |
| Country: Number of subjects enrolled | Japan: 21              |
| Country: Number of subjects enrolled | Korea, Republic of: 40 |
| Country: Number of subjects enrolled | Peru: 5                |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 10             |
| Country: Number of subjects enrolled | Portugal: 7            |
| Country: Number of subjects enrolled | Russian Federation: 46 |
| Country: Number of subjects enrolled | Serbia: 13             |
| Country: Number of subjects enrolled | Singapore: 3           |
| Country: Number of subjects enrolled | Spain: 8               |
| Country: Number of subjects enrolled | Taiwan: 6              |
| Country: Number of subjects enrolled | Türkiye: 2             |
| Country: Number of subjects enrolled | Ukraine: 28            |
| Country: Number of subjects enrolled | United States: 6       |
| Worldwide total number of subjects   | 369                    |
| EEA total number of subjects         | 90                     |

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)                      | 284 |
| From 65 to 84 years                       | 85  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

This study was conducted at 113 centers in 29 countries worldwide (Argentina, Australia, Belgium, Brazil, Bulgaria, China, Croatia, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Peru, Poland, Portugal, Republic of Korea, Russia, Serbia, Singapore, Spain, Taiwan, Turkey, UK, Ukraine and USA)

### Period 1

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

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |  |
|------------------|--|
| <b>Arm title</b> | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) |
|------------------|--|

Arm description:

Lapatinib 1000 mg PO once daily + Trastuzumab (loading dose of 8 mg/kg) followed by the maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Lapatinib                        |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Prolonged-release tablet, Tablet |
| Routes of administration               | Oral use                         |

Dosage and administration details:

1000 mg by mouth once a day

|  |                     |
|--|---------------------|
| Investigational medicinal product name | Aromatase Inhibitor |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Tablet              |
| Routes of administration               | Oral use            |

Dosage and administration details:

Aromatase inhibitor (either letrozole, anastrozole, or exemestane) of investigator's choice given by mouth once daily

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

Dosage and administration details:

Loading dose of 8 mg/kg IV followed by the maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks)

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Lapatinib + Aromatase Inhibitor (AI) |
|------------------|--------------------------------------|

Arm description:

Lapatinib 1500 mg PO once daily + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |                     |
|--|---------------------|
| Investigational medicinal product name | Aromatase Inhibitor |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Tablet              |
| Routes of administration               | Oral use            |

Dosage and administration details:

Aromatase inhibitor (either letrozole, anastrozole, or exemestane) of investigator's choice given by mouth once daily

|  |                                  |
|--|----------------------------------|
| Investigational medicinal product name | Lapatinib                        |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Prolonged-release tablet, Tablet |
| Routes of administration               | Oral use                         |

Dosage and administration details:

1500 mg by mouth once a day

|                  |  |
|------------------|--|
| <b>Arm title</b> | Trastuzumab + Aromatase Inhibitor (AI) |
|------------------|--|

Arm description:

Trastuzumab (loading dose of 8 mg/kg) followed by maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.

|  |                     |
|--|---------------------|
| Arm type                               | Active comparator   |
| Investigational medicinal product name | Aromatase Inhibitor |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Tablet              |
| Routes of administration               | Oral use            |

Dosage and administration details:

Aromatase inhibitor (either letrozole, anastrozole, or exemestane) of investigator's choice given by mouth once daily

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

Dosage and administration details:

Loading dose of 8 mg/kg IV followed by the maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks)

| <b>Number of subjects in period 1</b>              | Lapatinib +<br>Trastuzumab +<br>Aromatase Inhibitor<br>(AI) | Lapatinib +<br>Aromatase Inhibitor<br>(AI) | Trastuzumab +<br>Aromatase Inhibitor<br>(AI) |
|--|---|--|--|
| Started  | 124   | 123  | 122  |
| Safety Set   | 123   | 123  | 121  |
| Completed  | 64  | 64   | 55   |
| Not completed                                      | 60  | 59   | 67   |
| Physician decision                                 | 1   | -  | -  |
| Consent withdrawn by subject                       | 4   | 2  | 2  |
| Data unavailable due to regulatory issues          | 2   | -  | 2  |
| Subject Reached Protocol-Defined Stopping Criteria | 49  | 49   | 59   |

|                   |   |   |   |
|-------------------|---|---|---|
| Lost to follow-up | 4 | 8 | 4 |
|-------------------|---|---|---|

## Baseline characteristics

### Reporting groups

|  |  |
|--|--|
| Reporting group title  | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) |
| Reporting group description:<br>Lapatinib 1000 mg PO once daily + Trastuzumab (loading dose of 8 mg/kg) followed by the maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily. |  |
| Reporting group title  | Lapatinib + Aromatase Inhibitor (AI)               |
| Reporting group description:<br>Lapatinib 1500 mg PO once daily + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.  |  |
| Reporting group title  | Trastuzumab + Aromatase Inhibitor (AI)             |
| Reporting group description:<br>Trastuzumab (loading dose of 8 mg/kg) followed by maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.                                       |  |

| Reporting group values                             | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) | Lapatinib + Aromatase Inhibitor (AI) | Trastuzumab + Aromatase Inhibitor (AI) |
|--|--|--------------------------------------|--|
| Number of subjects                                 | 124  | 123                                  | 122                                    |
| Age categorical<br>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)                               | 92   | 92                                   | 100                                    |
| From 65-84 years                                   | 32   | 31                                   | 22                                     |
| 85 years and over                                  | 0  | 0                                    | 0                                      |
| Age Continuous<br>Units: Years                     |  |                                      |  |
| arithmetic mean                                    | 56.9   | 57.1                                 | 54.9                                   |
| standard deviation                                 | ± 11.15  | ± 9.98                               | ± 10.10                                |
| Sex: Female, Male<br>Units: Participants           |  |                                      |  |
| Female   | 124  | 123                                  | 122                                    |
| Male   | 0  | 0                                    | 0                                      |
| Race (NIH/OMB)<br>Units: Subjects                  |  |                                      |  |
| American Indian or Alaska Native                   | 1  | 1                                    | 1                                      |
| Asian  | 31   | 31                                   | 32                                     |
| Native Hawaiian or Other Pacific Islander          | 0  | 0                                    | 0                                      |
| Black or African American                          | 3  | 4                                    | 3                                      |
| White  | 89   | 85                                   | 84                                     |
| More than one race                                 | 0  | 2                                    | 2                                      |
| Unknown or Not Reported                            | 0  | 0                                    | 0                                      |

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>   | Total |  |  |
| Number of subjects  | 369   |  |  |
| Age categorical<br>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)  | 284   |  |  |
| From 65-84 years  | 85    |  |  |
| 85 years and over   | 0     |  |  |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation | -     |  |  |
| Sex: Female, Male<br>Units: Participants                                |       |  |  |
| Female  | 369   |  |  |
| Male  | 0     |  |  |
| Race (NIH/OMB)<br>Units: Subjects                                       |       |  |  |
| American Indian or Alaska Native  | 3     |  |  |
| Asian   | 94    |  |  |
| Native Hawaiian or Other Pacific<br>Islander                            | 0     |  |  |
| Black or African American   | 10    |  |  |
| White   | 258   |  |  |
| More than one race  | 4     |  |  |
| Unknown or Not Reported   | 0     |  |  |



## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) |
| Reporting group description:<br>Lapatinib 1000 mg PO once daily + Trastuzumab (loading dose of 8 mg/kg) followed by the maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily. |  |
| Reporting group title  | Lapatinib + Aromatase Inhibitor (AI)               |
| Reporting group description:<br>Lapatinib 1500 mg PO once daily + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.  |  |
| Reporting group title  | Trastuzumab + Aromatase Inhibitor (AI)             |
| Reporting group description:<br>Trastuzumab (loading dose of 8 mg/kg) followed by maintenance dose of 6 mg/kg IV every 3 weeks (q3weeks) + an Aromatase Inhibitor (AI) of Investigator's choice PO once daily.                                       |  |

### Primary: Progression Free Survival (PFS) events in Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) vs. Trastuzumab + Aromatase Inhibitor (AI)

|   |  |
|---|--|
| End point title   | Progression Free Survival (PFS) events in Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) vs. Trastuzumab + Aromatase Inhibitor (AI) <sup>[1]</sup> |
| End point description:<br>The Number of Participants with Progression free survival (PFS) events in the Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) arm vs. Trastuzumab + Aromatase Inhibitor (AI) arm was based on assessments by the Investigator. |  |
| End point type  | Primary  |
| End point timeframe:<br>From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up approximately 5 years  |  |

#### Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only descriptive analysis performed

| End point values                                  | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) | Trastuzumab + Aromatase Inhibitor (AI) |  |  |
|---|--|--|--|--|
| Subject group type                                | Reporting group                                    | Reporting group                        |  |  |
| Number of subjects analysed                       | 120  | 117                                    |  |  |
| Units: Participants                               |  |  |  |  |
| Disease progression or died (event)               | 62   | 75                                     |  |  |
| Censored, follow-up for disease progression ended | 7  | 3                                      |  |  |
| Censored, f/p for disease progression ongoing     | 51   | 39                                     |  |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | PFS of lap.+trast.+AI vs. trast.+AI   |
| Statistical analysis description:   |   |
| Null hypothesis H0: $\lambda \geq 1$ or to reject it in favor of the alternative hypothesis HA: $\lambda < 1$ , where $\lambda$ is the hazard ratio (HR) between Treatment Group A and Treatment Group B for progression-free survival. |   |
| Comparison groups   | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis   | 237   |
| Analysis specification  | Pre-specified   |
| Analysis type   |   |
| P-value   | = 0.0063 [2]  |
| Method  | Logrank   |
| Parameter estimate  | Hazard ratio (HR)   |
| Point estimate  | 0.62  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.45  |
| upper limit   | 0.88  |

Notes:

[2] - Pike estimate of the treatment hazard ratio, <1 indicates a lower risk compared with trastuzumab + AI.

### Primary: Median Kaplan Meier estimates for PFS in Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) vs. Trastuzumab + Aromatase Inhibitor (AI)

|                 |  |
|-----------------|--|
| End point title | Median Kaplan Meier estimates for PFS in Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) vs. Trastuzumab + Aromatase Inhibitor (AI) <sup>[3][4]</sup> |
|-----------------|--|

End point description:

Progression free survival (PFS) was defined as the interval of time between the date of randomization and the earliest date of disease progression (with radiological evidence) or death from any cause, or to the date of censor. Disease progression was based on assessments by the Investigator.

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

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up approximately 5 years

Notes:

[3] - 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: The primary endpoint evaluated PFS comparing treatment group A (lapatinib+trastuzumab+AI) vs. treatment group B (trastuzumab+AI)

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The primary endpoint evaluated PFS comparing treatment group A (lapatinib+trastuzumab+AI) vs. treatment group B (trastuzumab+AI)

| <b>End point values</b>          | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) | Trastuzumab + Aromatase Inhibitor (AI) |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group                                    | Reporting group                        |  |  |
| Number of subjects analysed      | 120  | 117                                    |  |  |
| Units: Months                    |  |  |  |  |
| median (confidence interval 95%) | 11.0 (8.3 to 13.8)                                 | 5.6 (5.4 to 8.3)                       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression free survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression free survival (PFS) |
|-----------------|---------------------------------|

End point description:

Progression free survival (PFS) was defined as the interval of time between the date of randomization and the earliest date of disease progression (with radiological evidence) or death from any cause, or to the date of censor. Disease progression was based on assessments by the Investigator.

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

End point timeframe:

From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up approximately 11 years

| End point values                 | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) | Lapatinib + Aromatase Inhibitor (AI) | Trastuzumab + Aromatase Inhibitor (AI) |  |
|----------------------------------|--|--------------------------------------|--|--|
| Subject group type               | Reporting group                                    | Reporting group                      | Reporting group                        |  |
| Number of subjects analysed      | 124  | 123                                  | 122                                    |  |
| Units: Months                    |  |                                      |  |  |
| median (confidence interval 95%) | 11.1 (10.0 to 15.3)                                | 8.3 (7.1 to 11.0)                    | 5.7 (5.5 to 8.3)                       |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | PFS of lap.+trast.+AI vs. trast.+AI   |
| Comparison groups                       | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 246   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.59  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.44  |
| upper limit                             | 0.79  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | PFS of lap.+trast.+AI vs. lap.+AI   |
| Comparison groups                       | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Lapatinib + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 247   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.68  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.51  |
| upper limit                             | 0.92  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | PFS of lap.+AI vs. trast.+AI  |
| Comparison groups                       | Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 245   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.87  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.66  |
| upper limit                             | 1.15  |

## Secondary: Overall Survival (OS)

|                        |  |
|------------------------|--|
| End point title        | Overall Survival (OS)  |
| End point description: | The Number of Participants with Overall Survival (OS) events was based on assessments by the Investigator. |
| End point type         | Secondary  |
| End point timeframe:   | From date of randomization until date of death from any cause, assessed up approximately 11 years          |

| End point values            | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) | Lapatinib + Aromatase Inhibitor (AI) | Trastuzumab + Aromatase Inhibitor (AI) |  |
|-----------------------------|--|--------------------------------------|--|--|
| Subject group type          | Reporting group                                    | Reporting group                      | Reporting group                        |  |
| Number of subjects analysed | 124  | 123                                  | 122                                    |  |
| Units: Participants         |  |                                      |  |  |
| Death                       | 38   | 45                                   | 39                                     |  |
| Censored, follow-up ended   | 86   | 78                                   | 83                                     |  |
| Censored, follow-up ongoing | 0  | 0                                    | 0                                      |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Response Rate (ORR)

|  |                             |
|--|-----------------------------|
| End point title  | Overall Response Rate (ORR) |
| End point description:   |                             |
| Overall Response Rate (ORR) was defined as the proportion of participants achieving either a Complete Response (CR) or Partial Response (PR). The ORR was calculated from the Investigator's assessment of response based on RECIST 1.1. Subjects with an unknown or missing response were treated as non-responders; i.e. they were included in the denominator when calculating the percentages. Subjects who do not have measurable disease contributed to the Response Rate based analyses, for the evaluation of CR, SD and PD. |                             |
| End point type   | Secondary                   |
| End point timeframe:   |                             |
| Up approximately 11 years  |                             |

| End point values                  | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) | Lapatinib + Aromatase Inhibitor (AI) | Trastuzumab + Aromatase Inhibitor (AI) |  |
|-----------------------------------|--|--------------------------------------|--|--|
| Subject group type                | Reporting group                                    | Reporting group                      | Reporting group                        |  |
| Number of subjects analysed       | 124  | 123                                  | 122                                    |  |
| Units: Percentage of Participants |  |                                      |  |  |
| number (confidence interval 95%)  | 32.3 (24.2 to 41.2)                                | 22.8 (15.7 to 31.2)                  | 17.2 (11.0 to 25.1)                    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical Benefit Rate (CBR)

|  |                             |
|--|-----------------------------|
| End point title  | Clinical Benefit Rate (CBR) |
| End point description:   |                             |
| Clinical Benefit Rate (CBR) was defined as the percentage of patients with evidence of Complete Response (CR), Partial Response (PR), or maintaining Stable Disease (SD) for at least 6 months while on study, according to the investigator assessment of response per RECIST 1.1 criteria. |                             |

|                           |           |
|---------------------------|-----------|
| End point type            | Secondary |
| End point timeframe:      |           |
| Up approximately 11 years |           |

| End point values                  | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) | Lapatinib + Aromatase Inhibitor (AI) | Trastuzumab + Aromatase Inhibitor (AI) |  |
|-----------------------------------|--|--------------------------------------|--|--|
| Subject group type                | Reporting group                                    | Reporting group                      | Reporting group                        |  |
| Number of subjects analysed       | 124  | 123                                  | 122                                    |  |
| Units: Percentage of Participants |  |                                      |  |  |
| number (confidence interval 95%)  | 51.6 (42.5 to 60.7)                                | 43.1 (34.2 to 52.3)                  | 34.4 (26.1 to 43.6)                    |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Response

|   |                  |
|---|------------------|
| End point title   | Time to Response |
| End point description:  |                  |
| Time to Response (TTR) was defined as the time from randomization to the earliest date of Complete Response (CR) or Partial Response (PR) |                  |
| End point type  | Secondary        |
| End point timeframe:  |                  |
| From date of randomization until the earliest date of Complete Response (CR) or Partial Response (PR), assessed up approximately 11 years |                  |

| End point values              | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) | Lapatinib + Aromatase Inhibitor (AI) | Trastuzumab + Aromatase Inhibitor (AI) |  |
|-------------------------------|--|--------------------------------------|--|--|
| Subject group type            | Reporting group                                    | Reporting group                      | Reporting group                        |  |
| Number of subjects analysed   | 40   | 28                                   | 21                                     |  |
| Units: Days                   |  |                                      |  |  |
| median (full range (min-max)) | 85.0 (72 to 1031)                                  | 86.5 (65 to 1175)                    | 86.0 (67 to 337)                       |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DoR)

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

End point description:

Duration of Response (DOR) was defined as the duration between the date of first documented Complete Response (CR) or Partial Response (PR) and the date of first documented sign of Progressive Disease or Death, or to the date of censor.

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

End point timeframe:

From first documented evidence of CR or PR (the response prior to confirmation) until time of documented disease progression or death due to any cause, whichever comes first, assessed up approximately 11 years

| End point values                 | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) | Lapatinib + Aromatase Inhibitor (AI) | Trastuzumab + Aromatase Inhibitor (AI) |  |
|----------------------------------|--|--------------------------------------|--|--|
| Subject group type               | Reporting group                                    | Reporting group                      | Reporting group                        |  |
| Number of subjects analysed      | 40   | 28                                   | 21                                     |  |
| Units: Months                    |  |                                      |  |  |
| median (confidence interval 95%) | 22.5 (11.1 to 33.1)                                | 11.1 (5.6 to 999)                    | 11.8 (5.4 to 28.1)                     |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean change in the Quality of Life (QoL) Status Relative to Baseline FACT-B Overall and Subscale Scores at Last On treatment Assessment

|                 |   |
|-----------------|---|
| End point title | Mean change in the Quality of Life (QoL) Status Relative to Baseline FACT-B Overall and Subscale Scores at Last On treatment Assessment |
|-----------------|---|

End point description:

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire. It is a 37-item (27 general questions and 10 breast cancer specific questions) self-reporting instrument consisting of 5 dimensions: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and a breast cancer subscale (BCS). The followings were the score ranges for each self-reporting subscale: • PWB : 0-28 • SWB : 0-28 • EWB : 0-24 • FWB : 0-28 • BCS : 0-40 FACT-B Total Outcome Index (TOI) = PWB + FWB + BCS (range:0 - 96) FACT-B Total Score = PWB + SWB + EWB + FWB + BCS (range:0-148) FACT-G Total Score = PWB + SWB + EWB + FWB (range:0-108). For all the FACIT scales and symptom indices, the higher the score the better QoL

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

End point timeframe:

Day 1 (pre-dose), up approximately 11 years

| <b>End point values</b>             | Lapatinib +<br>Trastuzumab +<br>Aromatase<br>Inhibitor (AI) | Lapatinib +<br>Aromatase<br>Inhibitor (AI) | Trastuzumab +<br>Aromatase<br>Inhibitor (AI) |  |
|-------------------------------------|---|--|--|--|
| Subject group type                  | Reporting group   | Reporting group                            | Reporting group                              |  |
| Number of subjects analysed         | 115   | 113  | 110  |  |
| Units: score on a scale             |   |  |  |  |
| least squares mean (standard error) |   |  |  |  |
| FACT-B total score                  | -4.2 (± 1.48)   | -6.3 (± 1.51)                              | -2.4 (± 1.51)                                |  |
| FACT-G total score                  | -4.3 (± 1.22)   | -5.9 (± 1.24)                              | -2.8 (± 1.24)                                |  |
| FACT-B trial outcome Index (TOI)    | -3.3 (± 1.05)   | -4.2 (± 1.07)                              | -0.6 (± 1.07)                                |  |
| Physical well-being (PWB)           | -2.0 (± 0.48)   | -2.1 (± 0.49)                              | -0.5 (± 0.49)                                |  |
| Social family wellbeing (SWB)       | -0.5 (± 0.50)   | -1.5 (± 0.50)                              | -0.9 (± 0.51)                                |  |
| Emotional wellbeing (EWB)           | -0.4 (± 0.40)   | -0.6 (± 0.40)                              | -1.0 (± 0.41)                                |  |
| Functional wellbeing (FWB)          | -1.3 (± 0.45)   | -1.7 (± 0.46)                              | -0.3 (± 0.46)                                |  |
| Breast cancer subscale (BCS)        | 0.0 (± 0.47)  | -0.5 (± 0.47)                              | 0.4 (± 0.48)                                 |  |

## Statistical analyses

| <b>Statistical analysis title</b>       | FACT-G total score  |
|---|---|
| Comparison groups                       | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 225   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -1.5  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -4.92   |
| upper limit                             | 1.92  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 1.739   |

| <b>Statistical analysis title</b>       | FACT-B total score  |
|---|---|
| Comparison groups                       | Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 223   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -3.9  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -8.09   |
| upper limit                             | 0.29  |



|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 2.13                       |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | FACT-B total score  |
| Comparison groups                       | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 225   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -1.79   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -5.95   |
| upper limit                             | 2.36  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 2.111   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | FACT-G total score  |
| Comparison groups                       | Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 223   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -3.1  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -6.55   |
| upper limit                             | 0.34  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 1.751   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Physical well-being (PWB)   |
| Comparison groups                       | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 225   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -1.46   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -2.82                      |
| upper limit          | -0.11                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.69                       |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | FACT-B trial outcome index (TOI)  |
| Comparison groups                       | Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 223   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -3.61   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -6.59   |
| upper limit                             | -0.64   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 1.512   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | FACT-B trial outcome index (TOI)  |
| Comparison groups                       | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 225   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -2.7  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -5.66   |
| upper limit                             | 0.25  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 1.502   |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Physical well-being (PWB)   |
| Comparison groups                 | Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 223                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           |                            |
| Parameter estimate                      | Least square difference    |
| Point estimate                          | -1.54                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -2.9                       |
| upper limit                             | -0.18                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.693                      |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Social family wellbeing (SWB)   |
| Comparison groups                       | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 225   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | 0.39  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -1.01   |
| upper limit                             | 1.79  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.711   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Social family wellbeing (SWB)   |
| Comparison groups                       | Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 223   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -0.55   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -1.96   |
| upper limit                             | 0.86  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.715   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Emotional wellbeing (EWB)   |
| Comparison groups                       | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 225   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | 0.54  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.57   |
| upper limit                             | 1.66  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.568   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Emotional wellbeing (EWB)   |
| Comparison groups                       | Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 223   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | 0.4   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -0.72   |
| upper limit                             | 1.53  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.571   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Functional wellbeing (FWB)  |
| Comparison groups                       | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 225   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -0.99   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2.26   |
| upper limit                             | 0.28  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.646   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Functional wellbeing (FWB)  |
| Comparison groups                       | Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 223   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -1.32   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2.6  |
| upper limit                             | -0.04   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.649   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Breast cancer subscale (BCS)  |
| Comparison groups                       | Lapatinib + Trastuzumab + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 225   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -0.35   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -1.66   |
| upper limit                             | 0.95  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.665   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Breast cancer subscale (BCS)  |
| Comparison groups                       | Lapatinib + Aromatase Inhibitor (AI) v Trastuzumab + Aromatase Inhibitor (AI) |
| Number of subjects included in analysis | 223   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| Parameter estimate                      | Least square difference   |
| Point estimate                          | -0.83   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -2.14                      |
| upper limit          | 0.48                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.668                      |

### Post-hoc: All collected deaths

|                 |                      |
|-----------------|----------------------|
| End point title | All collected deaths |
|-----------------|----------------------|

End point description:

Pre-treatment deaths were collected from day of participant's informed consent to the day before first dose of study medication.

On-treatment deaths were collected from first dose of study medication to 30 days after last dose of study medication (on-treatment), up to approximately 131 months.

Deaths were collected in the post treatment survival follow up from 31 days after last dose of study medication until the end of the study, up to approximately 132 months.

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Pre-treatment deaths: Up to 28 days prior to treatment. On-treatment deaths: Up to 131 months. Post-treatment deaths: up to 132 months.

| End point values            | Lapatinib +<br>Trastuzumab +<br>Aromatase<br>Inhibitor (AI) | Lapatinib +<br>Aromatase<br>Inhibitor (AI) | Trastuzumab +<br>Aromatase<br>Inhibitor (AI) |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group   | Reporting group                            | Reporting group                              |  |
| Number of subjects analysed | 124   | 123  | 122  |  |
| Units: Participants         |   |  |  |  |
| Pre-treatment deaths        | 0   | 0  | 0  |  |
| On-treatment deaths         | 5   | 8  | 5  |  |
| Post-treatment deaths       | 33  | 37   | 34   |  |
| All deaths                  | 38  | 45   | 39   |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days, up to a maximum duration of approximately 131 months.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Lapatinib (1000mg) + Trastuzumab (6 mg/kg) + AI |
|-----------------------|---|

Reporting group description:

Lapatinib (1000mg) + Trastuzumab (6 mg/kg) + AI

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Trastuzumab (6 mg/kg) + AI |
|-----------------------|----------------------------|

Reporting group description:

Trastuzumab (6 mg/kg) + AI

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Lapatinib (1500mg) + AI |
|-----------------------|-------------------------|

Reporting group description:

Lapatinib (1500mg) + AI

| Serious adverse events  | Lapatinib (1000mg) + Trastuzumab (6 mg/kg) + AI | Trastuzumab (6 mg/kg) + AI | Lapatinib (1500mg) + AI |
|---|---|----------------------------|-------------------------|
| Total subjects affected by serious adverse events                   |   |                            |                         |
| subjects affected / exposed   | 27 / 123 (21.95%)                               | 14 / 121 (11.57%)          | 23 / 123 (18.70%)       |
| number of deaths (all causes)                                       | 5   | 5                          | 8                       |
| number of deaths resulting from adverse events                      | 1   | 0                          | 1                       |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |                            |                         |
| Metastases to lung  |   |                            |                         |
| subjects affected / exposed   | 1 / 123 (0.81%)                                 | 0 / 121 (0.00%)            | 0 / 123 (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                   |
| Papillary thyroid cancer  |   |                            |                         |
| subjects affected / exposed   | 1 / 123 (0.81%)                                 | 0 / 121 (0.00%)            | 0 / 123 (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                   |
| Ovarian epithelial cancer   |   |                            |                         |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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                                   |                 |                 |                 |
| Thrombophlebitis                                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Asthenia   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 0 / 123 (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           |
| Organ failure  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 1           |
| Pain   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Immune system disorders                              |                 |                 |                 |
| Iodine allergy                                       |                 |                 |                 |
| subjects affected / exposed                          | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Drug hypersensitivity                                |                 |                 |                 |
| subjects affected / exposed                          | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |                 |
| Haemoptysis  |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 0 / 123 (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           |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Hydrothorax                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Pneumothorax                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| 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 failure                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 0 / 123 (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           |
| Psychiatric disorders                           |                 |                 |                 |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 0 / 123 (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           |
| Investigations                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Alanine aminotransferase increased<br>subjects affected / exposed | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to<br>treatment / all                | 1 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| Aspartate aminotransferase<br>increased                           |                 |                 |                 |
| subjects affected / exposed                                       | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to<br>treatment / all                | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| Ejection fraction decreased                                       |                 |                 |                 |
| subjects affected / exposed                                       | 7 / 123 (5.69%) | 2 / 121 (1.65%) | 1 / 123 (0.81%) |
| occurrences causally related to<br>treatment / all                | 6 / 8           | 2 / 2           | 1 / 1           |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural<br>complications                 |                 |                 |                 |
| Femur fracture  |                 |                 |                 |
| subjects affected / exposed                                       | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture  |                 |                 |                 |
| subjects affected / exposed                                       | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| Ligament sprain   |                 |                 |                 |
| subjects affected / exposed                                       | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to<br>treatment / all                | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| Muscle strain   |                 |                 |                 |
| subjects affected / exposed                                       | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to<br>treatment / all                | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |
| Post procedural inflammation                                      |                 |                 |                 |
| subjects affected / exposed                                       | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to<br>treatment / all                | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                     | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Spinal compression fracture<br>subjects affected / exposed  | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders   |                 |                 |                 |
| Acute myocardial infarction<br>subjects affected / exposed  | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure<br>subjects affected / exposed              | 1 / 123 (0.81%) | 1 / 121 (0.83%) | 0 / 123 (0.00%) |
| occurrences causally related to<br>treatment / all          | 1 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardio-respiratory arrest<br>subjects affected / exposed    | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 0 / 123 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 1           | 0 / 0           |
| Left ventricular dysfunction<br>subjects affected / exposed | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to<br>treatment / all          | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiogenic shock<br>subjects affected / exposed            | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 1           |
| Nervous system disorders                                    |                 |                 |                 |
| Cerebrovascular accident<br>subjects affected / exposed     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Cognitive disorder<br>subjects affected / exposed           | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 1           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Headache  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Speech disorder                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 0 / 123 (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           |
| Neuropathy peripheral                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 0 / 123 (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           |
| Intracranial aneurysm                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 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 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anaemia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Anal fissure                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Ascites   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| Enteritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis acute                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Hepatic failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Renal and urinary disorders                     |                 |                 |                 |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelocaliectasis                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Rheumatoid arthritis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 0 / 123 (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 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Infections and infestations                     |                 |                 |                 |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 0 / 123 (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                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteomyelitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Lower respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Herpes zoster                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 123 (0.00%) | 0 / 121 (0.00%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 3 / 123 (2.44%) | 2 / 121 (1.65%) | 1 / 123 (0.81%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 1 / 121 (0.83%) | 0 / 123 (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           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Pyuria  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Diabetic ketoacidosis                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Diabetic metabolic decompensation               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Hypercalcaemia                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 123 (0.00%) | 1 / 121 (0.83%) | 0 / 123 (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           |
| Hypocalcaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |
| Hypokalaemia                                    |                 |                 |                 |
| subjects affected / exposed                     | 2 / 123 (1.63%) | 0 / 121 (0.00%) | 0 / 123 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypomagnesaemia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 123 (0.81%) | 0 / 121 (0.00%) | 0 / 123 (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           |

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

| <b>Non-serious adverse events</b>                     | Lapatinib (1000mg) + Trastuzumab (6 mg/kg) + AI | Trastuzumab (6 mg/kg) + AI | Lapatinib (1500mg) + AI |
|---|---|----------------------------|-------------------------|
| Total subjects affected by non-serious adverse events |   |                            |                         |
| subjects affected / exposed                           | 113 / 123 (91.87%)                              | 86 / 121 (71.07%)          | 107 / 123 (86.99%)      |
| Investigations  |   |                            |                         |
| Alanine aminotransferase increased                    |   |                            |                         |
| subjects affected / exposed                           | 11 / 123 (8.94%)                                | 9 / 121 (7.44%)            | 20 / 123 (16.26%)       |
| occurrences (all)                                     | 15  | 11                         | 26                      |
| Aspartate aminotransferase increased                  |   |                            |                         |
| subjects affected / exposed                           | 11 / 123 (8.94%)                                | 11 / 121 (9.09%)           | 22 / 123 (17.89%)       |
| occurrences (all)                                     | 12  | 12                         | 28                      |
| Ejection fraction decreased                           |   |                            |                         |
| subjects affected / exposed                           | 10 / 123 (8.13%)                                | 3 / 121 (2.48%)            | 3 / 123 (2.44%)         |
| occurrences (all)                                     | 10  | 4                          | 3                       |
| Blood bilirubin increased                             |   |                            |                         |



|   |                         |                         |                         |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)  | 3 / 123 (2.44%)<br>3    | 1 / 121 (0.83%)<br>1    | 8 / 123 (6.50%)<br>8    |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)                                | 5 / 123 (4.07%)<br>5    | 9 / 121 (7.44%)<br>9    | 7 / 123 (5.69%)<br>8    |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)  | 12 / 123 (9.76%)<br>13  | 3 / 121 (2.48%)<br>3    | 13 / 123 (10.57%)<br>14 |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)                                  | 9 / 123 (7.32%)<br>13   | 8 / 121 (6.61%)<br>9    | 4 / 123 (3.25%)<br>5    |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                               | 10 / 123 (8.13%)<br>11  | 9 / 121 (7.44%)<br>9    | 10 / 123 (8.13%)<br>14  |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 9 / 123 (7.32%)<br>13   | 15 / 121 (12.40%)<br>22 | 21 / 123 (17.07%)<br>25 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)                     | 8 / 123 (6.50%)<br>11   | 8 / 121 (6.61%)<br>8    | 7 / 123 (5.69%)<br>7    |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)   | 6 / 123 (4.88%)<br>6    | 3 / 121 (2.48%)<br>7    | 7 / 123 (5.69%)<br>10   |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 15 / 123 (12.20%)<br>16 | 6 / 121 (4.96%)<br>36   | 7 / 123 (5.69%)<br>8    |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 15 / 123 (12.20%)<br>17 | 12 / 121 (9.92%)<br>16  | 19 / 123 (15.45%)<br>20 |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)   | 8 / 123 (6.50%)<br>8    | 5 / 121 (4.13%)<br>5    | 5 / 123 (4.07%)<br>5    |

|  |                          |                         |                          |
|--|--------------------------|-------------------------|--------------------------|
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)              | 7 / 123 (5.69%)<br>11    | 6 / 121 (4.96%)<br>8    | 6 / 123 (4.88%)<br>6     |
| Gastrointestinal disorders   |                          |                         |                          |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 9 / 123 (7.32%)<br>9     | 9 / 121 (7.44%)<br>9    | 7 / 123 (5.69%)<br>8     |
| Cheilitis<br>subjects affected / exposed<br>occurrences (all)            | 7 / 123 (5.69%)<br>8     | 0 / 121 (0.00%)<br>0    | 1 / 123 (0.81%)<br>1     |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 16 / 123 (13.01%)<br>17  | 1 / 121 (0.83%)<br>1    | 19 / 123 (15.45%)<br>28  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)           | 23 / 123 (18.70%)<br>29  | 5 / 121 (4.13%)<br>5    | 16 / 123 (13.01%)<br>26  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 28 / 123 (22.76%)<br>32  | 13 / 121 (10.74%)<br>17 | 28 / 123 (22.76%)<br>46  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)            | 8 / 123 (6.50%)<br>10    | 0 / 121 (0.00%)<br>0    | 4 / 123 (3.25%)<br>4     |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 87 / 123 (70.73%)<br>235 | 11 / 121 (9.09%)<br>11  | 64 / 123 (52.03%)<br>130 |
| Respiratory, thoracic and mediastinal disorders                          |                          |                         |                          |
| Cough<br>subjects affected / exposed<br>occurrences (all)                | 12 / 123 (9.76%)<br>14   | 17 / 121 (14.05%)<br>20 | 16 / 123 (13.01%)<br>18  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)             | 7 / 123 (5.69%)<br>7     | 8 / 121 (6.61%)<br>8    | 9 / 123 (7.32%)<br>10    |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)            | 10 / 123 (8.13%)<br>11   | 0 / 121 (0.00%)<br>0    | 8 / 123 (6.50%)<br>10    |
| Nasal dryness  |                          |                         |                          |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 7 / 123 (5.69%)<br>8 | 1 / 121 (0.83%)<br>1 | 3 / 123 (2.44%)<br>3 |
| Skin and subcutaneous tissue disorders             |                      |                      |                      |
| Pruritus   |                      |                      |                      |
| subjects affected / exposed                        | 11 / 123 (8.94%)     | 2 / 121 (1.65%)      | 11 / 123 (8.94%)     |
| occurrences (all)                                  | 14                   | 2                    | 13                   |
| Alopecia   |                      |                      |                      |
| subjects affected / exposed                        | 14 / 123 (11.38%)    | 2 / 121 (1.65%)      | 8 / 123 (6.50%)      |
| occurrences (all)                                  | 14                   | 2                    | 8                    |
| Dermatitis acneiform                               |                      |                      |                      |
| subjects affected / exposed                        | 16 / 123 (13.01%)    | 2 / 121 (1.65%)      | 11 / 123 (8.94%)     |
| occurrences (all)                                  | 25                   | 2                    | 15                   |
| Dry skin   |                      |                      |                      |
| subjects affected / exposed                        | 11 / 123 (8.94%)     | 0 / 121 (0.00%)      | 11 / 123 (8.94%)     |
| occurrences (all)                                  | 12                   | 0                    | 11                   |
| Palmar-plantar erythrodysesthesia<br>syndrome      |                      |                      |                      |
| subjects affected / exposed                        | 13 / 123 (10.57%)    | 1 / 121 (0.83%)      | 11 / 123 (8.94%)     |
| occurrences (all)                                  | 13                   | 1                    | 11                   |
| Rash maculo-papular                                |                      |                      |                      |
| subjects affected / exposed                        | 7 / 123 (5.69%)      | 0 / 121 (0.00%)      | 7 / 123 (5.69%)      |
| occurrences (all)                                  | 10                   | 0                    | 11                   |
| Rash   |                      |                      |                      |
| subjects affected / exposed                        | 43 / 123 (34.96%)    | 3 / 121 (2.48%)      | 36 / 123 (29.27%)    |
| occurrences (all)                                  | 64                   | 3                    | 51                   |
| Skin fissures                                      |                      |                      |                      |
| subjects affected / exposed                        | 7 / 123 (5.69%)      | 2 / 121 (1.65%)      | 3 / 123 (2.44%)      |
| occurrences (all)                                  | 8                    | 2                    | 3                    |
| Psychiatric disorders                              |                      |                      |                      |
| Insomnia   |                      |                      |                      |
| subjects affected / exposed                        | 5 / 123 (4.07%)      | 4 / 121 (3.31%)      | 12 / 123 (9.76%)     |
| occurrences (all)                                  | 5                    | 4                    | 14                   |
| Musculoskeletal and connective tissue<br>disorders |                      |                      |                      |
| Back pain  |                      |                      |                      |
| subjects affected / exposed                        | 9 / 123 (7.32%)      | 10 / 121 (8.26%)     | 12 / 123 (9.76%)     |
| occurrences (all)                                  | 10                   | 13                   | 13                   |
| Arthralgia   |                      |                      |                      |

|   |                         |                         |                         |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 22 / 123 (17.89%)<br>29 | 15 / 121 (12.40%)<br>20 | 19 / 123 (15.45%)<br>23 |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)                         | 7 / 123 (5.69%)<br>8    | 7 / 121 (5.79%)<br>8    | 4 / 123 (3.25%)<br>4    |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                           | 7 / 123 (5.69%)<br>7    | 8 / 121 (6.61%)<br>12   | 6 / 123 (4.88%)<br>7    |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                 | 11 / 123 (8.94%)<br>13  | 5 / 121 (4.13%)<br>6    | 12 / 123 (9.76%)<br>14  |
| Infections and infestations   |                         |                         |                         |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 8 / 123 (6.50%)<br>10   | 10 / 121 (8.26%)<br>13  | 6 / 123 (4.88%)<br>7    |
| Paronychia<br>subjects affected / exposed<br>occurrences (all)                        | 39 / 123 (31.71%)<br>73 | 0 / 121 (0.00%)<br>0    | 21 / 123 (17.07%)<br>35 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 13 / 123 (10.57%)<br>22 | 7 / 121 (5.79%)<br>8    | 8 / 123 (6.50%)<br>15   |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 7 / 123 (5.69%)<br>8    | 5 / 121 (4.13%)<br>5    | 0 / 123 (0.00%)<br>0    |
| Metabolism and nutrition disorders  |                         |                         |                         |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                      | 9 / 123 (7.32%)<br>16   | 0 / 121 (0.00%)<br>0    | 8 / 123 (6.50%)<br>9    |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                | 22 / 123 (17.89%)<br>25 | 4 / 121 (3.31%)<br>4    | 18 / 123 (14.63%)<br>20 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 20 February 2013 | Amendment 1: Country specific amendment for France. Protocol appendices 3 and 4 were updated to include the Diarrhea Management Guidelines and Dermatological Assessment Guidelines   |
| 23 July 2013     | Amendment 2: Global amendment allowed entry of subjects who were receiving later lines of therapies, including at least one prior trastuzumab and chemotherapy regimen. Updates were made to inclusion/exclusion criteria; changes were made to prohibited medications (removal of restrictions around bisphosphonate use, allowance of denosumab, clarification on permitted use of radiotherapy, additions to prohibited medications table).  |
| 29 January 2014  | Amendment 3: Country-specific amendment for France. Updates to protocol was done to include management guidelines for treatment of prolonged QT/QTc and a reference to a list of known drugs that cause QT/QTc prolongations were provided. Updates made to Dermatological Assessment Guidelines.   |
| 10 December 2014 | Amendment 4: Country-specific amendment for China. Updates were done to protocol to adjust the time period of SAE collection in accordance with China regulations   |
| 18 March 2016    | Amendment 5: Global amendment: Since study EGF114299 is a post-approval commitment to both the CHMP and the FDA, these regulatory agencies were consulted in light of the study enrollment challenges in this subject population (CHMP in October 2015 and FDA in September 2015). The primary endpoint was changed from OS to PFS. In addition, the amendment introduced the following changes: Secondary endpoints were updated, and survival follow-up removed. The revised sample size was changed to approximately 345 subjects. Country-specific amendments No. 3 and 4 for France and China, respectively, were included in this global amendment for harmonization purposes as it also applies to all countries. Protocol appendices 3 and 4 were updated to include Diarrhea Management Guidelines and Dermatological Assessment Guidelines. Protocol Section 5.8.4 and Section 6.2 were updated to include management guidelines for prolonged QT/QTc and to provide a reference to a list of drugs known to cause QT/QTc prolongations. Protocol Section 7.3.3.5 was updated to adjust the time period of SAE collection in accordance with China regulations. |
| 19 May 2016      | Amendment 6: Deleted or replaced references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship; administrative changes to align with Novartis processes and procedures.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.  
Please use <https://www.novctrd.com/#/> for complete trial results.

Notes:

