



## Clinical trial results:

### A Randomized, Multicentre, Open-Label, Phase III Study of Lapatinib plus Capecitabine versus Trastuzumab plus Capecitabine in Subjects with Anthracycline- or Taxane-Exposed ErbB2-Positive Metastatic Breast Cancer

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/CtrdWeb/home.nov> for complete trial results.

## Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2008-000673-38                |
| Trial protocol           | DE FR ES BE IT SE DK HU GB GR |
| Global end of trial date | 22 March 2018                 |

## Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 07 April 2019 |
| First version publication date | 07 April 2019 |

## Trial information

### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | EGF111438 |
|-----------------------|-----------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00820222 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |                                                                                           |
|------------------------------|-------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Novartis Pharma AG                                                                        |
| Sponsor organisation address | CH-4002, 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                       | 22 March 2018 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 22 March 2018 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of lapatinib plus capecitabine on incidence of central nervous system (CNS) metastases as site of first relapse as compared with trastuzumab plus capecitabine.

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                          | 14 April 2009 |
| 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 | Belgium: 4              |
| Country: Number of subjects enrolled | Denmark: 3              |
| Country: Number of subjects enrolled | France: 30              |
| Country: Number of subjects enrolled | Germany: 32             |
| Country: Number of subjects enrolled | Greece: 7               |
| Country: Number of subjects enrolled | Hungary: 20             |
| Country: Number of subjects enrolled | Italy: 47               |
| Country: Number of subjects enrolled | Poland: 86              |
| Country: Number of subjects enrolled | Russian Federation: 197 |
| Country: Number of subjects enrolled | Spain: 31               |
| Country: Number of subjects enrolled | Sweden: 8               |
| Country: Number of subjects enrolled | Thailand: 8             |
| Country: Number of subjects enrolled | United Kingdom: 64      |
| Country: Number of subjects enrolled | United States: 3        |
| Worldwide total number of subjects   | 540                     |
| EEA total number of subjects         | 332                     |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 447 |
| From 65 to 84 years                       | 93  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The study was terminated based on the IDMC recommendation in 2012 and collection of efficacy data was discontinued.

### Pre-assignment

Screening details:

An amended protocol allowed subjects to enroll in a Long Term Follow Up if they had evidence of clinical benefit but no local access to standard of care treatments. Subjects received study treatment until until disease progression, unacceptable toxicity, or participant withdrawal.

### 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 plus Capecitabine |

Arm description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) at approximately the same time every day, either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Participants also received capecitabine 2000 mg per meters squared (mg/m<sup>2</sup>) per day (divided and administered orally twice daily, 12 hours apart), for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.

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

Dosage and administration details:

Lapatinib 1250 mg once daily

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

Dosage and administration details:

Capecitabine 2000mg/m<sup>2</sup>/day, days 1-14, every 21 days

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Trastuzumab plus Capecitabine |
|------------------|-------------------------------|

Arm description:

Participants received an intravenous (IV) infusion of trastuzumab 8 mg/kilogram (kg) on Day 1, followed by a 6 mg/kg infusion every 3 weeks. Participants also received capecitabine 2500 mg/m<sup>2</sup> per day (divided and administered orally twice daily, 12 hours apart), for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.

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

|                                                                           |                     |
|---------------------------------------------------------------------------|---------------------|
| Investigational medicinal product name                                    | Trastuzumab         |
| Investigational medicinal product code                                    |                     |
| Other name                                                                |                     |
| Pharmaceutical forms                                                      | Powder for infusion |
| Routes of administration                                                  | Intravenous use     |
| Dosage and administration details:                                        |                     |
| Trastuzumab loading dose of 8mg/kg followed by 6mg/kg q3weekly infusions. |                     |
| Investigational medicinal product name                                    | Capecitabine        |
| Investigational medicinal product code                                    |                     |
| Other name                                                                |                     |
| Pharmaceutical forms                                                      | Tablet              |
| Routes of administration                                                  | Oral use            |
| Dosage and administration details:                                        |                     |
| Capecitabine 2500mg/m2/day, days 1-14, every 21 days                      |                     |

| <b>Number of subjects in period 1</b> | Lapatinib plus<br>Capecitabine | Trastuzumab plus<br>Capecitabine |
|---------------------------------------|--------------------------------|----------------------------------|
| Started                               | 271                            | 269                              |
| Completed                             | 95                             | 79                               |
| Not completed                         | 176                            | 190                              |
| Consent withdrawn by subject          | 19                             | 21                               |
| Physician decision                    | 93                             | 88                               |
| Sponsor Terminated Study              | 43                             | 65                               |
| Lost to follow-up                     | 10                             | 9                                |
| Unkown                                | 11                             | 7                                |

## Baseline characteristics

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Lapatinib plus Capecitabine |
|-----------------------|-----------------------------|

Reporting group description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) at approximately the same time every day, either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Participants also received capecitabine 2000 mg per meters squared (mg/m<sup>2</sup>) per day (divided and administered orally twice daily, 12 hours apart), for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Trastuzumab plus Capecitabine |
|-----------------------|-------------------------------|

Reporting group description:

Participants received an intravenous (IV) infusion of trastuzumab 8 mg/kilogram (kg) on Day 1, followed by a 6 mg/kg infusion every 3 weeks. Participants also received capecitabine 2500 mg/m<sup>2</sup> per day (divided and administered orally twice daily, 12 hours apart), for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.

| Reporting group values                             | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine | Total |
|----------------------------------------------------|-----------------------------|-------------------------------|-------|
| Number of subjects                                 | 271                         | 269                           | 540   |
| 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)                               | 237                         | 210                           | 447   |
| From 65-84 years                                   | 34                          | 59                            | 93    |
| 85 years and over                                  | 0                           | 0                             | 0     |
| Age continuous<br>Units: years                     |                             |                               |       |
| arithmetic mean                                    | 53.4                        | 55.8                          |       |
| standard deviation                                 | ± 10.23                     | ± 10.26                       | -     |
| Sex: Female, Male<br>Units: Subjects               |                             |                               |       |
| Female                                             | 271                         | 269                           | 540   |
| Male                                               | 0                           | 0                             | 0     |
| Race/Ethnicity, Customized<br>Units: Subjects      |                             |                               |       |
| White - White/Caucasian/European                   | 266                         | 260                           | 526   |
| White - Arabic/North African Heritage              | 0                           | 1                             | 1     |
| African American/African Heritage                  | 1                           | 1                             | 2     |
| Asian - Central/South Asian Heritage               | 1                           | 1                             | 2     |
| Asian - East Asian Heritage                        | 1                           | 2                             | 3     |
| Asian - South East Asian Heritage                  | 2                           | 3                             | 5     |

|                                              |   |   |   |
|----------------------------------------------|---|---|---|
| Native Hawaiian or other Pacific<br>Islander | 0 | 1 | 1 |
|----------------------------------------------|---|---|---|

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                               |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Lapatinib plus Capecitabine   |
| Reporting group description:<br>Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) at approximately the same time every day, either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. Participants also received capecitabine 2000 mg per meters squared (mg/m <sup>2</sup> ) per day (divided and administered orally twice daily, 12 hours apart), for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal. |                               |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Trastuzumab plus Capecitabine |
| Reporting group description:<br>Participants received an intravenous (IV) infusion of trastuzumab 8 mg/kilogram (kg) on Day 1, followed by a 6 mg/kg infusion every 3 weeks. Participants also received capecitabine 2500 mg/m <sup>2</sup> per day (divided and administered orally twice daily, 12 hours apart), for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.                                                                                         |                               |

### Primary: Number of participants with Central Nervous System (CNS) metastases (as assessed by independent review) as the site of first relapse

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Number of participants with Central Nervous System (CNS) metastases (as assessed by independent review) as the site of first relapse |
| End point description:<br>CNS relapse is defined as the appearance of $\geq 1$ enhancing lesion measuring $\geq 6$ millimeters (mm) on T1Weighted (T1W) Magnetic Resonance Imaging (MRI) without CNS symptoms that were considered to be unequivocal based on all relevant radiological features (e.g., associated T2W signal abnormality); the appearance of any enhancing lesion on T1W MRI with CNS symptoms; unequivocal finding of leptomeningeal disease (defined as the dissemination of cancer throughout the spinal fluid), with or without symptoms; and unequivocal finding of multifocal intraparenchymal lesions with or without symptoms. In the event of the appearance of a $< 6$ mm lesions(s) without CNS lesions, or equivocal findings potentially suggesting leptomeningeal disease, these findings were followed with a subsequent scan within 6 weeks. If unequivocal progression was determined with the subsequent scan and/or CNS symptoms occurred, then CNS relapse criteria were met. |                                                                                                                                      |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Primary                                                                                                                              |
| End point timeframe:<br>From randomization until disease progression, death, or discontinuation from the study (average of 10 months). Cut-off 11-Jun-2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                      |

| End point values            | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine |  |  |
|-----------------------------|-----------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group             | Reporting group               |  |  |
| Number of subjects analysed | 251                         | 250                           |  |  |
| Units: participants         | 8                           | 12                            |  |  |

## Statistical analyses

|                                         |                                                             |
|-----------------------------------------|-------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Comparison of CNS metastases                                |
| Comparison groups                       | Lapatinib plus Capecitabine v Trastuzumab plus Capecitabine |
| Number of subjects included in analysis | 501                                                         |
| Analysis specification                  | Pre-specified                                               |
| Analysis type                           |                                                             |
| P-value                                 | = 0.36                                                      |
| Method                                  | Odds Ratio                                                  |
| Parameter estimate                      | Odds ratio (OR)                                             |
| Point estimate                          | 0.65                                                        |
| Confidence interval                     |                                                             |
| level                                   | 95 %                                                        |
| sides                                   | 2-sided                                                     |
| lower limit                             | 0.26                                                        |
| upper limit                             | 1.63                                                        |

### Secondary: Progression free survival (PFS), as assessed by the investigator

|                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                              | Progression free survival (PFS), as assessed by the investigator |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                  |
| PFS is defined as the interval between the date of randomization and the earliest date of progressive disease (PD), or death due to any cause. PD is defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, compared with the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions based on investigator assessment of both CNS and non-CNS for response. |                                                                  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                               | Secondary                                                        |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                  |
| From randomization until disease progression, death, or discontinuation from the study (average of 10 months). Cut-off 11-Jun-2012                                                                                                                                                                                                                                                                                                           |                                                                  |

| End point values                 | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine |  |  |
|----------------------------------|-----------------------------|-------------------------------|--|--|
| Subject group type               | Reporting group             | Reporting group               |  |  |
| Number of subjects analysed      | 271                         | 269                           |  |  |
| Units: months                    |                             |                               |  |  |
| median (confidence interval 95%) | 6.60 (5.72 to 8.11)         | 8.05 (6.14 to 8.90)           |  |  |

### Statistical analyses

|                                   |                                                             |
|-----------------------------------|-------------------------------------------------------------|
| <b>Statistical analysis title</b> | Hazard Ratio for Progression Free Survival                  |
| Comparison groups                 | Lapatinib plus Capecitabine v Trastuzumab plus Capecitabine |

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 540                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| P-value                                 | = 0.021                    |
| Method                                  | Logrank                    |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 1.3                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 1.04                       |
| upper limit                             | 1.64                       |

Notes:

[1] - A HR > 1 indicates a higher risk for lapatinib+capecitabine compared with trastuzumab+capecitabine.

### Secondary: Time to first CNS progression, defined as the time from randomization until the date of documented CNS progression as the first site of relapse

|                 |                                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Time to first CNS progression, defined as the time from randomization until the date of documented CNS progression as the first site of relapse |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

CNS relapse is defined as the appearance of  $\geq 1$  enhancing lesion measuring  $\geq 6$  mm on T1W MRI without CNS symptoms that were considered to be unequivocal based on all relevant radiological features (e.g., associated T2W signal abnormality); the appearance of any enhancing lesion on T1W MRI with CNS symptoms; unequivocal finding of leptomeningeal disease (defined as the dissemination of cancer throughout the spinal fluid), with or without symptoms; and unequivocal finding of multifocal intraparenchymal lesions with or without symptoms. In the event of the appearance of a  $< 6$  mm lesions(s) without CNS lesions, or equivocal findings potentially suggesting leptomeningeal disease, these findings were followed with a subsequent scan within 6 weeks. If unequivocal progression was determined with the subsequent scan and/or CNS symptoms occurred, then CNS relapse criteria were met.

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

End point timeframe:

From randomization until the date of documented CNS progression (average of 10 months). Cut-off 11-Jun-2012

| End point values                     | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine |  |  |
|--------------------------------------|-----------------------------|-------------------------------|--|--|
| Subject group type                   | Reporting group             | Reporting group               |  |  |
| Number of subjects analysed          | 8                           | 12                            |  |  |
| Units: months                        |                             |                               |  |  |
| arithmetic mean (standard deviation) | 8.2 ( $\pm$ 6.78)           | 6.7 ( $\pm$ 6.94)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

Overall survival is defined as the time from randomization until death due to any cause or to the date of censor. In the absence of confirmation of death, survival time was to be censored at the time of the last investigator contact.

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

End point timeframe:

From randomization until death due to any cause (average of 10 months). Cut-off 11-Jun-2012

| End point values                 | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine |  |  |
|----------------------------------|-----------------------------|-------------------------------|--|--|
| Subject group type               | Reporting group             | Reporting group               |  |  |
| Number of subjects analysed      | 271                         | 269                           |  |  |
| Units: months                    |                             |                               |  |  |
| median (confidence interval 95%) | 22.7 (19.5 to 999)          | 27.3 (23.7 to 999)            |  |  |

## Statistical analyses

|                                         |                                                             |
|-----------------------------------------|-------------------------------------------------------------|
| Statistical analysis title              | Hazard Ratio for Overall Survival                           |
| Comparison groups                       | Lapatinib plus Capecitabine v Trastuzumab plus Capecitabine |
| Number of subjects included in analysis | 540                                                         |
| Analysis specification                  | Pre-specified                                               |
| Analysis type                           | superiority <sup>[2]</sup>                                  |
| P-value                                 | = 0.095                                                     |
| Method                                  | Logrank                                                     |
| Parameter estimate                      | Hazard ratio (HR)                                           |
| Point estimate                          | 1.34                                                        |
| Confidence interval                     |                                                             |
| level                                   | 95 %                                                        |
| sides                                   | 2-sided                                                     |
| lower limit                             | 0.95                                                        |
| upper limit                             | 1.9                                                         |

Notes:

[2] - A HR > 1 indicates a higher risk for lapatinib+capecitabine compared with trastuzumab+capecitabine.

## Secondary: Number of participants with Overall Response (OR), as assessed by the investigator

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Number of participants with Overall Response (OR), as assessed by the investigator |
|-----------------|------------------------------------------------------------------------------------|

End point description:

OR is defined as the number of participants with either a confirmed complete response (CR; disappearance of all target lesions) or partial response (PR: at least a 30% decrease in the sum of the LD of the target lesions, compared with the baseline sum LD). CR and PR were assessed per Response Evaluation Criteria in Solid Tumors (RECIST). To be assigned a status of PR or CR, a confirmatory disease assessment was to be performed 28 days (4 weeks) or greater after the criteria for response were first met. In addition, a bone scan must have been obtained to rule out the presence of new bone lesions or progression of existing bone lesions, even if the participant had no bone lesions present at Baseline. If a bone scan was performed at the time of initial response or near the time of response, the bone scan did not need to be repeated.

|                                                                                                                                    |           |
|------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                                     | Secondary |
| End point timeframe:                                                                                                               |           |
| From randomization until disease progression, death, or discontinuation from the study (average of 10 months). Cut-off 11-Jun-2012 |           |

| End point values            | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine |  |  |
|-----------------------------|-----------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group             | Reporting group               |  |  |
| Number of subjects analysed | 271                         | 269                           |  |  |
| Units: participants         |                             |                               |  |  |
| CR                          | 8                           | 12                            |  |  |
| PR                          | 65                          | 73                            |  |  |
| Overall Response (CR + PR)  | 73                          | 85                            |  |  |

### Statistical analyses

|                                         |                                                             |
|-----------------------------------------|-------------------------------------------------------------|
| Statistical analysis title              | Odds Ratio for Overall Response                             |
| Comparison groups                       | Lapatinib plus Capecitabine v Trastuzumab plus Capecitabine |
| Number of subjects included in analysis | 540                                                         |
| Analysis specification                  | Pre-specified                                               |
| Analysis type                           | superiority                                                 |
| P-value                                 | = 0.2731                                                    |
| Method                                  | Fisher exact                                                |
| Parameter estimate                      | Odds ratio (OR)                                             |
| Point estimate                          | 0.7984                                                      |
| Confidence interval                     |                                                             |
| level                                   | 95 %                                                        |
| sides                                   | 2-sided                                                     |
| lower limit                             | 0.5407                                                      |
| upper limit                             | 1.1771                                                      |

### Secondary: Number of participants with clinical benefit (CB)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Number of participants with clinical benefit (CB) |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                   |
| CB is defined as the number of participants with evidence of confirmed CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the LD of the target lesions, compared with the baseline sum LD) at any time or stable disease (SD, neither sufficient shrinkage to qualify for a PR nor sufficient increase to qualify for PD [defined as at least a 20% increase in the sum of the LD of target lesions, compared with the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions] based on investigator assessment), for at least 24 weeks. |                                                   |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Secondary                                         |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                   |
| From randomization until disease progression, death, or discontinuation from the study (average of 10 months). Cut-off 11-Jun-2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                   |

| <b>End point values</b>                     | Lapatinib plus<br>Capecitabine | Trastuzumab<br>plus<br>Capecitabine |  |  |
|---------------------------------------------|--------------------------------|-------------------------------------|--|--|
| Subject group type                          | Reporting group                | Reporting group                     |  |  |
| Number of subjects analysed                 | 271                            | 269                                 |  |  |
| Units: participants                         |                                |                                     |  |  |
| CR                                          | 8                              | 12                                  |  |  |
| PR                                          | 65                             | 73                                  |  |  |
| SD >= 24 weeks                              | 39                             | 33                                  |  |  |
| Clinical Benefit (CR + PR + SD >= 24 weeks) | 112                            | 118                                 |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Odds Ratio for Clinical Benefit                             |
|-----------------------------------------|-------------------------------------------------------------|
| Comparison groups                       | Lapatinib plus Capecitabine v Trastuzumab plus Capecitabine |
| Number of subjects included in analysis | 540                                                         |
| Analysis specification                  | Pre-specified                                               |
| Analysis type                           | superiority                                                 |
| P-value                                 | = 0.6106                                                    |
| Method                                  | Fisher exact                                                |
| Parameter estimate                      | Odds ratio (OR)                                             |
| Point estimate                          | 0.9016                                                      |
| Confidence interval                     |                                                             |
| level                                   | 95 %                                                        |
| sides                                   | 2-sided                                                     |
| lower limit                             | 0.6315                                                      |
| upper limit                             | 1.2866                                                      |

### Secondary: Duration of response

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Duration of response |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                      |
| Duration of response is defined as the time from the first documented evidence of CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the LD of the target lesions, compared with the baseline sum LD) until the first documented sign of PD (at least a 20% increase in the sum of the LD of target lesions, compared with the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions) or death due to breast cancer. In the absence of confirmation of death, survival time was to be censored at the time of the last investigator contact. |                      |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Secondary            |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                      |
| From the time of the first documented confirmed complete or partial response until disease progression or death, if sooner (average of 10 months). Cut-off 11-Jun-2012                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                      |

| End point values                 | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine |  |  |
|----------------------------------|-----------------------------|-------------------------------|--|--|
| Subject group type               | Reporting group             | Reporting group               |  |  |
| Number of subjects analysed      | 73                          | 85                            |  |  |
| Units: months                    |                             |                               |  |  |
| median (confidence interval 95%) | 6.2 (5.3 to 10.6)           | 8.4 (6.0 to 21.6)             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with CNS progression at any time

|                 |                                                         |
|-----------------|---------------------------------------------------------|
| End point title | Number of participants with CNS progression at any time |
|-----------------|---------------------------------------------------------|

End point description:

CNS progression was documented by a brain scan and was indicated by the investigator on the follow-up electronic Case Report Form. CNS relapse is defined as the appearance of  $\geq 1$  enhancing lesion measuring  $\geq 6$  mm on T1W MRI without CNS symptoms that were considered to be unequivocal based on all relevant radiological features (e.g., associated T2W signal abnormality); the appearance of any enhancing lesion on T1W MRI with CNS symptoms; unequivocal finding of leptomeningeal disease, with or without symptoms; and unequivocal finding of multifocal intraparenchymal lesions with or without symptoms. In the event of the appearance of a  $< 6$  mm lesions(s) without CNS lesions, or equivocal findings potentially suggesting leptomeningeal disease, these findings were followed with a subsequent scan within 6 weeks. If unequivocal progression was determined with the subsequent scan and/or CNS symptoms occurred, then CNS relapse criteria were met.

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

End point timeframe:

From the time of randomization until death due to any cause (average of 10 months). Cut-off 11-Jun-2012

| End point values            | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine |  |  |
|-----------------------------|-----------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group             | Reporting group               |  |  |
| Number of subjects analysed | 251                         | 250                           |  |  |
| Units: participants         | 17                          | 15                            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with qualitative and quantitative toxicities

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Number of participants with qualitative and quantitative toxicities |
|-----------------|---------------------------------------------------------------------|

End point description:

Qualitative and quantitative toxicities were measured as AEs. See the outcome measure entitled "Number of participants with the indicated Grade 3 or Grade 4 Adverse Events (AEs) occurring in  $\geq 2$  participants in either treatment arm" and the AE module of this results summary for a list of AEs

occurring in the study. An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

|                                                                                                                     |           |
|---------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                      | Secondary |
| End point timeframe:                                                                                                |           |
| From the first dose of study medication until 30 days after the last dose of study treatment (average of 10 months) |           |

| End point values            | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine |  |  |
|-----------------------------|-----------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group             | Reporting group               |  |  |
| Number of subjects analysed | 0 <sup>[3]</sup>            | 0 <sup>[4]</sup>              |  |  |
| Units: participants         |                             |                               |  |  |

Notes:

[3] - Reported in the AE module of this results summary.

[4] - Reported in the AE module of this results summary.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants expressing glucocorticoid receptor, phosphatase and tensin homolog (PTEN), phosphatidylinositide 3-kinase (PI3K)/AKT, protein 53 (P53), insulin-like growth factor-1 (IGF-1), and genes involved in cell cycle regulation

|                 |                                                                                                                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants expressing glucocorticoid receptor, phosphatase and tensin homolog (PTEN), phosphatidylinositide 3-kinase (PI3K)/AKT, protein 53 (P53), insulin-like growth factor-1 (IGF-1), and genes involved in cell cycle regulation |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Because the study terminated early, pharmacogenetic and biomarker analyses were not performed.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline             |           |

| End point values            | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine |  |  |
|-----------------------------|-----------------------------|-------------------------------|--|--|
| Subject group type          | Reporting group             | Reporting group               |  |  |
| Number of subjects analysed | 0 <sup>[5]</sup>            | 0 <sup>[6]</sup>              |  |  |
| Units: participants         |                             |                               |  |  |

Notes:

[5] - Because the study terminated early, pharmacogenetic and biomarker analyses were not performed.

[6] - Because the study terminated early, pharmacogenetic and biomarker analyses were not performed.

## Statistical analyses

**Secondary: Number of participants with the indicated Grade 3 or Grade 4 Adverse Events (AEs) occurring in  $\geq 2\%$  of participants in either treatment arm**

|                 |                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants with the indicated Grade 3 or Grade 4 Adverse Events (AEs) occurring in $\geq 2\%$ of participants in either treatment arm |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. The Investigator assessed whether the AE was related to study drug. AEs were graded using the Common Toxicity Criteria from the Cancer Therapy Evaluation Program, Division of Cancer Therapy, National Cancer Institute. Grades: 0=No AE or within normal limits; 1=Mild AE; 2=Moderate AE; 3=Severe and undesirable AE; 4=Life-threatening or disabling AE; 5=Death related to AE.

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

## End point timeframe:

From the first dose of study medication until 30 days after the last dose of study treatment (average of 10 months).

| End point values                           | Lapatinib plus Capecitabine | Trastuzumab plus Capecitabine |  |  |
|--------------------------------------------|-----------------------------|-------------------------------|--|--|
| Subject group type                         | Reporting group             | Reporting group               |  |  |
| Number of subjects analysed                | 270                         | 267                           |  |  |
| Units: participants                        |                             |                               |  |  |
| Palmar-plantar erythrodysesthesia syndrome | 29                          | 45                            |  |  |
| Diarrhoea                                  | 19                          | 22                            |  |  |
| Aspartate aminotransferase increased       | 11                          | 4                             |  |  |
| Neutropenia                                | 9                           | 18                            |  |  |
| Asthenia                                   | 9                           | 6                             |  |  |
| Fatigue                                    | 7                           | 4                             |  |  |
| Alanine aminotransferase increased         | 4                           | 6                             |  |  |
| Hypokalaemia                               | 3                           | 11                            |  |  |

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From randomization until up to and including 30 days after the last dose of study treatment (up to 7 years post randomization)

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 | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Lapatinib + Capecitabine |
|-----------------------|--------------------------|

Reporting group description:

Lapatinib + Capecitabine

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Trastuzumab + Capecitabine |
|-----------------------|----------------------------|

Reporting group description:

Trastuzumab + Capecitabine

| Serious adverse events                                              | Lapatinib + Capecitabine | Trastuzumab + Capecitabine |  |
|---------------------------------------------------------------------|--------------------------|----------------------------|--|
| Total subjects affected by serious adverse events                   |                          |                            |  |
| subjects affected / exposed                                         | 41 / 270 (15.19%)        | 51 / 267 (19.10%)          |  |
| number of deaths (all causes)                                       | 12                       | 3                          |  |
| number of deaths resulting from adverse events                      | 0                        | 1                          |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                          |                            |  |
| Tumour haemorrhage                                                  |                          |                            |  |
| subjects affected / exposed                                         | 0 / 270 (0.00%)          | 1 / 267 (0.37%)            |  |
| occurrences causally related to treatment / all                     | 0 / 0                    | 0 / 1                      |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0                      |  |
| Vascular disorders                                                  |                          |                            |  |
| Deep vein thrombosis                                                |                          |                            |  |
| subjects affected / exposed                                         | 1 / 270 (0.37%)          | 2 / 267 (0.75%)            |  |
| occurrences causally related to treatment / all                     | 1 / 1                    | 0 / 2                      |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0                      |  |
| Pelvic venous thrombosis                                            |                          |                            |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Thrombophlebitis                                     |                 |                 |  |
| subjects affected / exposed                          | 1 / 270 (0.37%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Thrombosis                                           |                 |                 |  |
| subjects affected / exposed                          | 0 / 270 (0.00%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vena cava thrombosis                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia                                             |                 |                 |  |
| subjects affected / exposed                          | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest pain                                           |                 |                 |  |
| subjects affected / exposed                          | 1 / 270 (0.37%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General physical health deterioration                |                 |                 |  |
| subjects affected / exposed                          | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Mucosal inflammation                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Non-cardiac chest pain                               |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 270 (0.00%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain                                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyrexia                                         |                 |                 |  |
| subjects affected / exposed                     | 3 / 270 (1.11%) | 3 / 267 (1.12%) |  |
| occurrences causally related to treatment / all | 4 / 6           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Cervical dysplasia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Aspiration                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleurisy                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleuritic pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Productive cough                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 270 (1.11%) | 6 / 267 (2.25%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 3 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood bilirubin increased                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ejection fraction decreased                     |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 270 (0.00%) | 3 / 267 (1.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Overdose                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Left ventricular dysfunction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebral haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Haemorrhagic stroke                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Headache                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Hemiplegia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neurological decompensation                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukopenia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenia                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 6 / 267 (2.25%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 5 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancytopenia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |

|                                                 |                 |                  |  |
|-------------------------------------------------|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastrointestinal disorders                      |                 |                  |  |
| Abdominal pain                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 267 (0.37%)  |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Abdominal pain upper                            |                 |                  |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Colitis                                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Constipation                                    |                 |                  |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 267 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Diarrhoea                                       |                 |                  |  |
| subjects affected / exposed                     | 4 / 270 (1.48%) | 10 / 267 (3.75%) |  |
| occurrences causally related to treatment / all | 5 / 6           | 10 / 10          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dyspepsia                                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastrointestinal inflammation                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastrooesophageal reflux disease                |                 |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea                                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting                                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Biliary colic                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Pruritus                                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash                                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stevens-Johnson syndrome                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Dysuria                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| Hydronephrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal chest pain                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myalgia                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                                                                                                                                           |                                           |                                           |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------------|--|
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | <br><br>0 / 270 (0.00%)<br>0 / 0<br>0 / 0 | <br><br>1 / 267 (0.37%)<br>0 / 1<br>0 / 0 |  |
| Cellulitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                | <br>1 / 270 (0.37%)<br>0 / 1<br>0 / 0     | <br>1 / 267 (0.37%)<br>0 / 1<br>0 / 0     |  |
| Clostridium difficile infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all           | <br>0 / 270 (0.00%)<br>0 / 0<br>0 / 0     | <br>1 / 267 (0.37%)<br>0 / 1<br>0 / 0     |  |
| Device related infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                  | <br>1 / 270 (0.37%)<br>0 / 1<br>0 / 0     | <br>0 / 267 (0.00%)<br>0 / 0<br>0 / 0     |  |
| Erysipelas<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                | <br>1 / 270 (0.37%)<br>0 / 2<br>0 / 0     | <br>1 / 267 (0.37%)<br>0 / 1<br>0 / 0     |  |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                           | <br>1 / 270 (0.37%)<br>0 / 1<br>0 / 0     | <br>1 / 267 (0.37%)<br>0 / 1<br>0 / 0     |  |
| Gastroenteritis bacterial<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | <br>1 / 270 (0.37%)<br>0 / 1<br>0 / 0     | <br>0 / 267 (0.00%)<br>0 / 0<br>0 / 0     |  |
| Infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                 | <br>1 / 270 (0.37%)<br>1 / 1<br>0 / 0     | <br>0 / 267 (0.00%)<br>0 / 0<br>0 / 0     |  |
| Localised infection                                                                                                                                                       |                                           |                                           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pharyngitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral infection                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral pharyngitis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperuricaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 3 / 267 (1.12%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypomagnesaemia                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Lapatinib +<br>Capecitabine | Trastuzumab +<br>Capecitabine |  |
|-------------------------------------------------------|-----------------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events |                             |                               |  |
| subjects affected / exposed                           | 241 / 270 (89.26%)          | 236 / 267 (88.39%)            |  |
| Investigations                                        |                             |                               |  |
| Alanine aminotransferase increased                    |                             |                               |  |
| subjects affected / exposed                           | 34 / 270 (12.59%)           | 35 / 267 (13.11%)             |  |
| occurrences (all)                                     | 45                          | 43                            |  |
| Aspartate aminotransferase increased                  |                             |                               |  |
| subjects affected / exposed                           | 33 / 270 (12.22%)           | 30 / 267 (11.24%)             |  |
| occurrences (all)                                     | 42                          | 39                            |  |
| Blood alkaline phosphatase increased                  |                             |                               |  |
| subjects affected / exposed                           | 17 / 270 (6.30%)            | 11 / 267 (4.12%)              |  |
| occurrences (all)                                     | 18                          | 15                            |  |
| Blood bilirubin increased                             |                             |                               |  |
| subjects affected / exposed                           | 19 / 270 (7.04%)            | 9 / 267 (3.37%)               |  |
| occurrences (all)                                     | 48                          | 15                            |  |

|                                                      |                    |                    |  |
|------------------------------------------------------|--------------------|--------------------|--|
| Nervous system disorders                             |                    |                    |  |
| Headache                                             |                    |                    |  |
| subjects affected / exposed                          | 15 / 270 (5.56%)   | 17 / 267 (6.37%)   |  |
| occurrences (all)                                    | 26                 | 17                 |  |
| Blood and lymphatic system disorders                 |                    |                    |  |
| Anaemia                                              |                    |                    |  |
| subjects affected / exposed                          | 22 / 270 (8.15%)   | 27 / 267 (10.11%)  |  |
| occurrences (all)                                    | 31                 | 38                 |  |
| Leukopenia                                           |                    |                    |  |
| subjects affected / exposed                          | 11 / 270 (4.07%)   | 21 / 267 (7.87%)   |  |
| occurrences (all)                                    | 19                 | 43                 |  |
| Neutropenia                                          |                    |                    |  |
| subjects affected / exposed                          | 38 / 270 (14.07%)  | 44 / 267 (16.48%)  |  |
| occurrences (all)                                    | 77                 | 91                 |  |
| General disorders and administration site conditions |                    |                    |  |
| Asthenia                                             |                    |                    |  |
| subjects affected / exposed                          | 46 / 270 (17.04%)  | 45 / 267 (16.85%)  |  |
| occurrences (all)                                    | 80                 | 63                 |  |
| Fatigue                                              |                    |                    |  |
| subjects affected / exposed                          | 26 / 270 (9.63%)   | 33 / 267 (12.36%)  |  |
| occurrences (all)                                    | 47                 | 41                 |  |
| Mucosal inflammation                                 |                    |                    |  |
| subjects affected / exposed                          | 21 / 270 (7.78%)   | 27 / 267 (10.11%)  |  |
| occurrences (all)                                    | 31                 | 42                 |  |
| Pyrexia                                              |                    |                    |  |
| subjects affected / exposed                          | 19 / 270 (7.04%)   | 25 / 267 (9.36%)   |  |
| occurrences (all)                                    | 28                 | 34                 |  |
| Gastrointestinal disorders                           |                    |                    |  |
| Abdominal pain upper                                 |                    |                    |  |
| subjects affected / exposed                          | 21 / 270 (7.78%)   | 16 / 267 (5.99%)   |  |
| occurrences (all)                                    | 27                 | 20                 |  |
| Diarrhoea                                            |                    |                    |  |
| subjects affected / exposed                          | 125 / 270 (46.30%) | 107 / 267 (40.07%) |  |
| occurrences (all)                                    | 300                | 209                |  |
| Dyspepsia                                            |                    |                    |  |

|                                                                                                              |                           |                           |  |
|--------------------------------------------------------------------------------------------------------------|---------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                             | 21 / 270 (7.78%)<br>24    | 19 / 267 (7.12%)<br>20    |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                                   | 82 / 270 (30.37%)<br>116  | 50 / 267 (18.73%)<br>79   |  |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)                                               | 16 / 270 (5.93%)<br>22    | 23 / 267 (8.61%)<br>27    |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                                 | 35 / 270 (12.96%)<br>60   | 27 / 267 (10.11%)<br>35   |  |
| Hepatobiliary disorders<br>Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all)           | 35 / 270 (12.96%)<br>67   | 26 / 267 (9.74%)<br>50    |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 22 / 270 (8.15%)<br>25    | 16 / 267 (5.99%)<br>16    |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                                                 | 11 / 270 (4.07%)<br>12    | 18 / 267 (6.74%)<br>18    |  |
| Skin and subcutaneous tissue disorders<br>Dry skin<br>subjects affected / exposed<br>occurrences (all)       | 15 / 270 (5.56%)<br>18    | 7 / 267 (2.62%)<br>7      |  |
| Nail disorder<br>subjects affected / exposed<br>occurrences (all)                                            | 21 / 270 (7.78%)<br>21    | 13 / 267 (4.87%)<br>14    |  |
| Palmar-plantar erythrodysesthesia syndrome<br>subjects affected / exposed<br>occurrences (all)               | 142 / 270 (52.59%)<br>238 | 160 / 267 (59.93%)<br>222 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                                                     | 66 / 270 (24.44%)<br>90   | 21 / 267 (7.87%)<br>26    |  |
| Musculoskeletal and connective tissue                                                                        |                           |                           |  |

|                                    |                   |                  |  |
|------------------------------------|-------------------|------------------|--|
| disorders                          |                   |                  |  |
| Back pain                          |                   |                  |  |
| subjects affected / exposed        | 16 / 270 (5.93%)  | 13 / 267 (4.87%) |  |
| occurrences (all)                  | 22                | 14               |  |
| Pain in extremity                  |                   |                  |  |
| subjects affected / exposed        | 14 / 270 (5.19%)  | 9 / 267 (3.37%)  |  |
| occurrences (all)                  | 15                | 15               |  |
| Metabolism and nutrition disorders |                   |                  |  |
| Decreased appetite                 |                   |                  |  |
| subjects affected / exposed        | 28 / 270 (10.37%) | 21 / 267 (7.87%) |  |
| occurrences (all)                  | 33                | 21               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                              |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 16 March 2009     | Country specific amendment was done for Sweden to modify exclusion criteria and allow subjects participating in Study LAP112867 who had short exposure to lapatinib to be eligible for this study.                                                                                     |
| 08 September 2010 | Changed description of the primary endpoint of the study and mandated independent review of baseline brain MRI scan for eligibility purpose and changes in analysis plan. Other amendments were made on inclusion/exclusion criteria and some study procedures and biomarker research. |
| 30 November 2011  | Minimum of one primary analysis utilizing an IDMC review to assess safety, PFS events and futility analysis on primary endpoint.                                                                                                                                                       |
| 10 September 2012 | The study was terminated based on the IDMC recommendation. However, this amendment allowed subjects to receive either lapatinib in combination with capecitabine or trastuzumab in combination with capecitabine where there was no local access to standard of care treatments.       |
| 24 March 2016     | Deleted or replaced references to GSK or its staff with that of Novartis/Novartis and its authorized agents.<br>Made 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/CtrdWeb/home.nov> for complete trial results.

Notes: