



## Clinical trial results:

**A randomized, multicenter open-label phase III study of neoadjuvant lapatinib, trastuzumab and their combination plus paclitaxel in women with HER2/ErbB2 positive primary breast cancer**

### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2006-000564-81                |
| Trial protocol           | FR DE BE GB LT GR HU ES IT SE |
| Global end of trial date | 23 December 2019              |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1              |
| This version publication date  | 06 January 2021 |
| First version publication date | 06 January 2021 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | EGF106903 |
|-----------------------|-----------|

#### Additional study identifiers

|                                    |                            |
|------------------------------------|----------------------------|
| ISRCTN number                      | -                          |
| ClinicalTrials.gov id (NCT number) | NCT00553358                |
| WHO universal trial number (UTN)   | -                          |
| Other trial identifiers            | CLAP016B2302: CLAP016B2302 |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland, CH-4002  |
| 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                       | 23 December 2019 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 23 December 2019 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate and compare the rate of pathological complete response (pCR) at the time of surgery in subjects with HER2 overexpressing or amplified operable breast cancer randomized to lapatinib followed by lapatinib plus paclitaxel versus trastuzumab followed by trastuzumab plus paclitaxel versus lapatinib in combination with trastuzumab followed by lapatinib, trastuzumab plus paclitaxel.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 05 January 2008 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 17          |
| Country: Number of subjects enrolled | Belgium: 33            |
| Country: Number of subjects enrolled | Brazil: 8              |
| Country: Number of subjects enrolled | Canada: 1              |
| Country: Number of subjects enrolled | Czechia: 10            |
| Country: Number of subjects enrolled | France: 22             |
| Country: Number of subjects enrolled | Germany: 49            |
| Country: Number of subjects enrolled | Hong Kong: 7           |
| Country: Number of subjects enrolled | Hungary: 11            |
| Country: Number of subjects enrolled | India: 12              |
| Country: Number of subjects enrolled | Italy: 16              |
| Country: Number of subjects enrolled | Korea, Republic of: 27 |
| Country: Number of subjects enrolled | Lithuania: 2           |
| Country: Number of subjects enrolled | Norway: 5              |
| Country: Number of subjects enrolled | Peru: 39               |
| Country: Number of subjects enrolled | Romania: 6             |
| Country: Number of subjects enrolled | Russian Federation: 25 |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | South Africa: 26   |
| Country: Number of subjects enrolled | Spain: 45          |
| Country: Number of subjects enrolled | Sweden: 2          |
| Country: Number of subjects enrolled | Taiwan: 57         |
| Country: Number of subjects enrolled | Ukraine: 23        |
| Country: Number of subjects enrolled | United Kingdom: 12 |
| Worldwide total number of subjects   | 455                |
| EEA total number of subjects         | 213                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 403 |
| From 65 to 84 years                       | 52  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

This was a parallel group, three-arm, randomized, multicenter, open-label phase III study (Figure 9-1). The study compared the efficacy and tolerability of neoadjuvant lapatinib and paclitaxel, versus trastuzumab and paclitaxel, versus the combination of lapatinib with trastuzumab and paclitaxel.

### 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 1000/750 mg + Trastuzumab 2 mg/kg |

Arm description:

Oral lapatinib 1000 mg daily plus trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly for 6 weeks, followed by lapatinib 750 mg daily plus trastuzumab (2 mg/kg IV weekly) plus weekly paclitaxel (80 mg/m<sup>2</sup> IV) for an additional 12 weeks

|  |  |
|--|--|
| Arm type                               | Experimental                                   |
| Investigational medicinal product name | Lapatinib + Trastuzumab                        |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solvent for parenteral use, Film-coated tablet |
| Routes of administration               | Oral use, Parenteral use                       |

Dosage and administration details:

Oral lapatinib (1000 mg daily) plus trastuzumab (4 mg/kg iv load followed by 2 mg/kg iv weekly) for 6 weeks, followed by lapatinib (750 mg daily) plus trastuzumab (2 mg/kg iv weekly) plus weekly paclitaxel (80 mg/m<sup>2</sup> iv) for an additional 12 weeks.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Lapatinib 1500 mg |
|------------------|-------------------|

Arm description:

Oral lapatinib (1500 milligrams [mg] daily) for 6 weeks, followed by lapatinib plus weekly paclitaxel (80 mg per meters squared [mg/m<sup>2</sup>]) intravenous (IV) for an additional 12 weeks

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Lapatinib          |
| Investigational medicinal product code | LAP016             |
| Other name                             | GW572016           |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Oral lapatinib (1500 mg daily) for 6 weeks, followed by lapatinib plus weekly paclitaxel (80 mg/m<sup>2</sup> iv) for an additional 12 weeks

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Trastuzumab 2 mg/kg |
|------------------|---------------------|

Arm description:

Trastuzumab (4 mg/kilograms [kg] IV load followed by 2 mg/kg IV weekly) for 6 weeks, followed by trastuzumab plus weekly paclitaxel (80 mg/m<sup>2</sup> IV) for an additional 12 weeks

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

|  |                            |
|--|----------------------------|
| Investigational medicinal product name | Trastuzumab                |
| Investigational medicinal product code |                            |
| Other name                             |                            |
| Pharmaceutical forms                   | Solvent for parenteral use |
| Routes of administration               | Parenteral use             |

Dosage and administration details:

Trastuzumab (4 mg/kg iv load followed by 2 mg/kg iv weekly) for 6 weeks, followed by trastuzumab plus weekly paclitaxel (80 mg/m<sup>2</sup> iv) for an additional 12 weeks

| Number of subjects in period 1                  | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |
|---|---|-------------------|---------------------|
|   |   |                   |                     |
| Started   | 152   | 154               | 149                 |
| Completed                                       | 73  | 58                | 61                  |
| Not completed                                   | 79  | 96                | 88                  |
| Died during clinical follow-up                  | 25  | 29                | 32                  |
| Randomized but did not receive treatment        | 3   | 3                 | 1                   |
| Died after clinical follow-up ended             | 1   | 2                 | -                   |
| Withdrew (survival only) – alive at end of f-up | 1   | 1                 | 1                   |
| Lost to follow-up                               | 22  | 26                | 18                  |
| Not dead but last f/up was prior to year 10     | 4   | 2                 | 2                   |
| Withdrew completely                             | 23  | 33                | 34                  |

## Baseline characteristics

### Reporting groups

|  |   |
|--|---|
| Reporting group title  | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg |
| Reporting group description:   |   |
| Oral lapatinib 1000 mg daily plus trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly for 6 weeks, followed by lapatinib 750 mg daily plus trastuzumab (2 mg/kg IV weekly) plus weekly paclitaxel (80 mg/m <sup>2</sup> IV) for an additional 12 weeks |   |
| Reporting group title  | Lapatinib 1500 mg                           |
| Reporting group description:   |   |
| Oral lapatinib (1500 milligrams [mg] daily) for 6 weeks, followed by lapatinib plus weekly paclitaxel (80 mg per meters squared [mg/m <sup>2</sup> ]) intravenous (IV) for an additional 12 weeks  |   |
| Reporting group title  | Trastuzumab 2 mg/kg                         |
| Reporting group description:   |   |
| Trastuzumab (4 mg/kilograms [kg] IV load followed by 2 mg/kg IV weekly) for 6 weeks, followed by trastuzumab plus weekly paclitaxel (80 mg/m <sup>2</sup> IV) for an additional 12 weeks   |   |

| Reporting group values                             | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |
|--|---|-------------------|---------------------|
| Number of subjects                                 | 152   | 154               | 149                 |
| Age categorical<br>Units: Participants             |   |                   |                     |
| 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)                               | 130   | 137               | 136                 |
| From 65-84 years                                   | 22  | 17                | 13                  |
| 85 years and over                                  | 0   | 0                 | 0                   |
| Age continuous<br>Units: years                     |   |                   |                     |
| median   | 50.0  | 50                | 49.0                |
| full range (min-max)                               | 25 to 80                                    | 28 to 79          | 23 to 77            |
| Gender categorical<br>Units: Subjects              |   |                   |                     |
| Female   | 152   | 154               | 149                 |
| Male   | 0   | 0                 | 0                   |
| GenderNIH<br>Units: Subjects                       |   |                   |                     |
| Female   | 152   | 154               | 149                 |
| Male   | 0   | 0                 | 0                   |
| Race/Ethnicity, Customized<br>Units: Subjects      |   |                   |                     |
| American Indian or Alaska Native                   | 15  | 13                | 14                  |
| Asian - Central/South                              | 5   | 7                 | 5                   |
| Asian - East                                       | 31  | 30                | 28                  |
| Asian - South East                                 | 2   | 0                 | 0                   |

|  |     |     |     |
|--|-----|-----|-----|
| Black or African American/African Heritage   | 4   | 0   | 4   |
| White - Arabic/North African Heritage  | 3   | 6   | 5   |
| White - Caucasian European Heritage  | 92  | 97  | 93  |
| Missing  | 0   | 1   | 0   |
| Number of participants with tumor cells of the indicated histologic grade  |     |     |     |
| Histologic grade, also called differentiation, refers to how much the tumor cells resemble normal cells of the same tissue type.   |     |     |     |
| Units: Subjects  |     |     |     |
| Well differentiated  | 5   | 2   | 5   |
| Moderately differentiated  | 63  | 56  | 53  |
| Poorly differentiated  | 64  | 73  | 68  |
| Differentiation cannot be assessed   | 20  | 22  | 23  |
| Missing  | 0   | 1   | 0   |
| Number of participants with lymph nodes (LNs) of the indicated clinical N stage  |     |     |     |
| Clinical N stage is an evaluation/staging of LN status through physical examination. N0, no regional LN metastasis; N1, metastasis to movable ipsilateral axillary LNs (IALNs); N2a, metastasis in IALNs fixed to one another (matted) or the other structures; N2b, metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary LN metastasis; N3a, metastasis in ipsilateral infraclavicular LNs; N3b, metastasis in ipsilateral internal mammary LNs fixed and axillary LN; N3c, metastasis in ipsilateral subclavicular LNs; Nx, not assessed. |     |     |     |
| Units: Subjects  |     |     |     |
| N 0  | 48  | 34  | 41  |
| N 1  | 80  | 95  | 85  |
| N2 (including N2a and N2b)   | 15  | 19  | 13  |
| N3 (including N3a, N3b, and N3c)   | 6   | 6   | 7   |
| N x  | 3   | 0   | 3   |
| Number of participants with the indicated IHC results  |     |     |     |
| An Immunohistochemistry (IHC) test gives a score of 0 to 3+, which indicates the amount of Human Epidermal Growth Factor (HER2) receptor proteins on the cancer cells in the sample tissue. A positive score (3+) indicates that HER2 receptor protein is present, a negative score (0-1+) indicates that no HER2 receptor protein is present, and an equivocal score (2+) indicates uncertainty and a result that is open for interpretation. Equivocal results require additional testing. "Not applicable" refers to the number of participants who did not have IHC testing done.                              |     |     |     |
| Units: Subjects  |     |     |     |
| Not applicable   | 61  | 60  | 53  |
| Equivocal: Score of 2+   | 8   | 9   | 5   |
| Positive: Score of 3+  | 76  | 81  | 89  |
| Negative: Score of 0-1+  | 3   | 0   | 1   |
| Non interpretable  | 4   | 4   | 1   |
| Number of participants with the indicated FISH results   |     |     |     |
| The Fluorescent In Situ Hybridization (FISH) assay was used to determine the overexpression and/or amplification of HER2 in the invasive component of the primary tumor. Amplified indicates that the cell is overexpressing copies of the HER2 gene. Not amplified indicates that there is no overexpression of copies of the HER2 gene. "Not applicable" refers to the number of participants who did not have the FISH assay performed.   |     |     |     |
| Units: Subjects  |     |     |     |
| Not applicable   | 41  | 38  | 42  |
| Amplified  | 109 | 115 | 105 |
| Not amplified  | 1   | 1   | 2   |
| Not interpretable  | 1   | 0   | 0   |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| AgeContinuous<br>Units: Years<br>median<br>full range (min-max)   | 50.0<br>25 to 80 | 50.0<br>28 to 79 | 49.0<br>23 to 77 |
| <b>Reporting group values</b>   | Total            |                  |                  |
| Number of subjects  | 455              |                  |                  |
| Age categorical<br>Units: Participants  |                  |                  |                  |
| In utero  | 0                |                  |                  |
| Preterm newborn infants<br>(gestational age < 37 wks)   | 0                |                  |                  |
| Newborns (0-27 days)  | 0                |                  |                  |
| Infants and toddlers (28 days-23<br>months)   | 0                |                  |                  |
| Children (2-11 years)   | 0                |                  |                  |
| Adolescents (12-17 years)   | 0                |                  |                  |
| Adults (18-64 years)  | 403              |                  |                  |
| From 65-84 years  | 52               |                  |                  |
| 85 years and over   | 0                |                  |                  |
| Age continuous<br>Units: years<br>median<br>full range (min-max)  | -                |                  |                  |
| Gender categorical<br>Units: Subjects   |                  |                  |                  |
| Female  | 455              |                  |                  |
| Male  | 0                |                  |                  |
| GenderNIH<br>Units: Subjects  |                  |                  |                  |
| Female  | 455              |                  |                  |
| Male  | 0                |                  |                  |
| Race/Ethnicity, Customized<br>Units: Subjects   |                  |                  |                  |
| American Indian or Alaska Native  | 42               |                  |                  |
| Asian - Central/South   | 17               |                  |                  |
| Asian - East  | 89               |                  |                  |
| Asian - South East  | 2                |                  |                  |
| Black or African American/African<br>Heritage   | 8                |                  |                  |
| White - Arabic/North African<br>Heritage  | 14               |                  |                  |
| White - Caucasian European<br>Heritage  | 282              |                  |                  |
| Missing   | 1                |                  |                  |
| Number of participants with tumor cells<br>of the indicated histologic grade  |                  |                  |                  |
| Histologic grade, also called differentiation, refers to how much the tumor cells resemble normal cells of<br>the same tissue type. |                  |                  |                  |
| Units: Subjects   |                  |                  |                  |
| Well differentiated   | 12               |                  |                  |
| Moderately differentiated   | 172              |                  |                  |
| Poorly differentiated   | 205              |                  |                  |
| Differentiation cannot be assessed  | 65               |                  |                  |



|  |     |  |  |
|--|-----|--|--|
| Missing  | 1   |  |  |
| Number of participants with lymph nodes (LNs) of the indicated clinical N stage  |     |  |  |
| Clinical N stage is an evaluation/staging of LN status through physical examination. N0, no regional LN metastasis; N1, metastasis to movable ipsilateral axillary LNs (IALNs); N2a, metastasis in IALNs fixed to one another (matted) or the other structures; N2b, metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary LN metastasis; N3a, metastasis in ipsilateral infraclavicular LNs; N3b, metastasis in ipsilateral internal mammary LNs fixed and axillary LN; N3c, metastasis in ipsilateral subclavicular LNs; Nx, not assessed. |     |  |  |
| Units: Subjects  |     |  |  |
| N 0  | 123 |  |  |
| N 1  | 260 |  |  |
| N2 (including N2a and N2b)   | 47  |  |  |
| N3 (including N3a, N3b, and N3c)   | 19  |  |  |
| N x  | 6   |  |  |
| Number of participants with the indicated IHC results  |     |  |  |
| An Immunohistochemistry (IHC) test gives a score of 0 to 3+, which indicates the amount of Human Epidermal Growth Factor (HER2) receptor proteins on the cancer cells in the sample tissue. A positive score (3+) indicates that HER2 receptor protein is present, a negative score (0-1+) indicates that no HER2 receptor protein is present, and an equivocal score (2+) indicates uncertainty and a result that is open for interpretation. Equivocal results require additional testing. "Not applicable" refers to the number of participants who did not have IHC testing done.                              |     |  |  |
| Units: Subjects  |     |  |  |
| Not applicable   | 174 |  |  |
| Equivocal: Score of 2+   | 22  |  |  |
| Positive: Score of 3+  | 246 |  |  |
| Negative: Score of 0-1+  | 4   |  |  |
| Non interpretable  | 9   |  |  |
| Number of participants with the indicated FISH results   |     |  |  |
| The Fluorescent In Situ Hybridization (FISH) assay was used to determine the overexpression and/or amplification of HER2 in the invasive component of the primary tumor. Amplified indicates that the cell is overexpressing copies of the HER2 gene. Not amplified indicates that there is no overexpression of copies of the HER2 gene. "Not applicable" refers to the number of participants who did not have the FISH assay performed.   |     |  |  |
| Units: Subjects  |     |  |  |
| Not applicable   | 121 |  |  |
| Amplified  | 329 |  |  |
| Not amplified  | 4   |  |  |
| Not interpretable  | 1   |  |  |
| AgeContinuous  |     |  |  |
| Units: Years   |     |  |  |
| median   |     |  |  |
| full range (min-max)   | -   |  |  |

## Subject analysis sets

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Intent to treat    |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

Intent-to-Treat (ITT) Population: all participants randomized to treatment, except for those who withdrew their consent to use any of their data (permitted by law in certain countries) prior to receiving any study medication

|  |                 |  |  |
|--|-----------------|--|--|
| <b>Reporting group values</b>  | Intent to treat |  |  |
| Number of subjects   | 455             |  |  |
| Age categorical<br>Units: Participants   |                 |  |  |
| In utero   | 0               |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks)  | 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)   | 403             |  |  |
| From 65-84 years   | 52              |  |  |
| 85 years and over  | 0               |  |  |
| Age continuous<br>Units: years   |                 |  |  |
| median   | 50.0            |  |  |
| full range (min-max)   | 23 to 80        |  |  |
| Gender categorical<br>Units: Subjects  |                 |  |  |
| Female   | 455             |  |  |
| Male   | 0               |  |  |
| GenderNIH<br>Units: Subjects   |                 |  |  |
| Female   |                 |  |  |
| Male   |                 |  |  |
| Race/Ethnicity, Customized<br>Units: Subjects  |                 |  |  |
| American Indian or Alaska Native   |                 |  |  |
| Asian - Central/South  |                 |  |  |
| Asian - East   |                 |  |  |
| Asian - South East   |                 |  |  |
| Black or African American/African Heritage   |                 |  |  |
| White - Arabic/North African Heritage  |                 |  |  |
| White - Caucasian European Heritage  |                 |  |  |
| Missing  |                 |  |  |
| Number of participants with tumor cells of the indicated histologic grade  |                 |  |  |
| Histologic grade, also called differentiation, refers to how much the tumor cells resemble normal cells of the same tissue type. |                 |  |  |
| Units: Subjects  |                 |  |  |
| Well differentiated  |                 |  |  |
| Moderately differentiated  |                 |  |  |
| Poorly differentiated  |                 |  |  |
| Differentiation cannot be assessed   |                 |  |  |
| Missing  |                 |  |  |
| Number of participants with lymph nodes (LNs) of the indicated clinical N stage  |                 |  |  |
| Clinical N stage is an evaluation/staging of LN status through physical examination. N0, no regional LN                          |                 |  |  |

metastasis; N1, metastasis to movable ipsilateral axillary LNs (IALNs); N2a, metastasis in IALNs fixed to one another (matted) or the other structures; N2b, metastasis only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary LN metastasis; N3a, metastasis in ipsilateral infraclavicular LNs; N3b, metastasis in ipsilateral internal mammary LNs fixed and axillary LN; N3c, metastasis in ipsilateral subclavicular LNs; Nx, not assessed.

|                                  |  |  |  |
|----------------------------------|--|--|--|
| Units: Subjects                  |  |  |  |
| N 0                              |  |  |  |
| N 1                              |  |  |  |
| N2 (including N2a and N2b)       |  |  |  |
| N3 (including N3a, N3b, and N3c) |  |  |  |
| N x                              |  |  |  |

|   |  |  |  |
|---|--|--|--|
| Number of participants with the indicated IHC results |  |  |  |
|---|--|--|--|

An Immunohistochemistry (IHC) test gives a score of 0 to 3+, which indicates the amount of Human Epidermal Growth Factor (HER2) receptor proteins on the cancer cells in the sample tissue. A positive score (3+) indicates that HER2 receptor protein is present, a negative score (0-1+) indicates that no HER2 receptor protein is present, and an equivocal score (2+) indicates uncertainty and a result that is open for interpretation. Equivocal results require additional testing. "Not applicable" refers to the number of participants who did not have IHC testing done.

|                         |  |  |  |
|-------------------------|--|--|--|
| Units: Subjects         |  |  |  |
| Not applicable          |  |  |  |
| Equivocal: Score of 2+  |  |  |  |
| Positive: Score of 3+   |  |  |  |
| Negative: Score of 0-1+ |  |  |  |
| Non interpretable       |  |  |  |

|  |  |  |  |
|--|--|--|--|
| Number of participants with the indicated FISH results |  |  |  |
|--|--|--|--|

The Fluorescent In Situ Hybridization (FISH) assay was used to determine the overexpression and/or amplification of HER2 in the invasive component of the primary tumor. Amplified indicates that the cell is overexpressing copies of the HER2 gene. Not amplified indicates that there is no overexpression of copies of the HER2 gene. "Not applicable" refers to the number of participants who did not have the FISH assay performed.

|                   |  |  |  |
|-------------------|--|--|--|
| Units: Subjects   |  |  |  |
| Not applicable    |  |  |  |
| Amplified         |  |  |  |
| Not amplified     |  |  |  |
| Not interpretable |  |  |  |

|                      |          |  |  |
|----------------------|----------|--|--|
| AgeContinuous        |          |  |  |
| Units: Years         |          |  |  |
| median               | 50       |  |  |
| full range (min-max) | 23 to 80 |  |  |

## End points

### End points reporting groups

|  |   |
|--|---|
| Reporting group title  | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg |
| Reporting group description:<br>Oral lapatinib 1000 mg daily plus trastuzumab 4 mg/kg IV load followed by 2 mg/kg IV weekly for 6 weeks, followed by lapatinib 750 mg daily plus trastuzumab (2 mg/kg IV weekly) plus weekly paclitaxel (80 mg/m <sup>2</sup> IV) for an additional 12 weeks |   |
| Reporting group title  | Lapatinib 1500 mg                           |
| Reporting group description:<br>Oral lapatinib (1500 milligrams [mg] daily) for 6 weeks, followed by lapatinib plus weekly paclitaxel (80 mg per meters squared [mg/m <sup>2</sup> ]) intravenous (IV) for an additional 12 weeks  |   |
| Reporting group title  | Trastuzumab 2 mg/kg                         |
| Reporting group description:<br>Trastuzumab (4 mg/kilograms [kg] IV load followed by 2 mg/kg IV weekly) for 6 weeks, followed by trastuzumab plus weekly paclitaxel (80 mg/m <sup>2</sup> IV) for an additional 12 weeks   |   |
| Subject analysis set title   | Intent to treat                             |
| Subject analysis set type  | Intention-to-treat                          |
| Subject analysis set description:<br>Intent-to-Treat (ITT) Population: all participants randomized to treatment, except for those who withdrew their consent to use any of their data (permitted by law in certain countries) prior to receiving any study medication                        |   |

### Primary: Number of participants with pathological complete response (pCR) at the time of surgery

|   |   |
|---|---|
| End point title   | Number of participants with pathological complete response (pCR) at the time of surgery |
| End point description:<br>Pathological complete response is defined as no invasive cancer in the breast or only non-invasive in situ cancer in the breast specimen. Surgical breast and axillary node resection specimens were evaluated for pathologic tumor response according to National Surgical Adjuvant Breast and Bowel Project (NSABP) guidelines, which do not take into account the histological nodal status. |   |
| End point type  | Primary   |
| End point timeframe:<br>Weeks 20 to 22  |   |

| End point values            | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|-----------------------------|---|-------------------|---------------------|--|
| Subject group type          | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed | 152   | 154               | 149                 |  |
| Units: participants         | 78  | 38                | 44                  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Participants with pCR at the time of surgery |
| Comparison groups          | Lapatinib 1500 mg v Trastuzumab 2 mg/kg      |

|   |                                     |
|---|-------------------------------------|
| Number of subjects included in analysis | 303                                 |
| Analysis specification                  | Pre-specified                       |
| Analysis type                           |                                     |
| P-value                                 | = 0.3416                            |
| Method                                  | Binomial                            |
| Parameter estimate                      | Percentage of participants with pCR |
| Point estimate                          | -4.85                               |
| Confidence interval                     |                                     |
| level                                   | Other: 97.5 %                       |
| sides                                   | 2-sided                             |
| lower limit                             | -17.6                               |
| upper limit                             | 8.16                                |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Participants with pCR at the time of surgery                      |
| Comparison groups                       | Trastuzumab 2 mg/kg v Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg |
| Number of subjects included in analysis | 301   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | = 0.0001  |
| Method                                  | Binomial  |
| Parameter estimate                      | Percentage of participants with pCR                               |
| Point estimate                          | 21.79   |
| Confidence interval                     |   |
| level                                   | Other: 97.5 %   |
| sides                                   | 2-sided   |
| lower limit                             | 9.08  |
| upper limit                             | 34.23   |

## Secondary: Number of participants with overall response at Week 6

|   |  |
|---|--|
| End point title   | Number of participants with overall response at Week 6 |
| End point description:  |  |
| The number of participants with overall response (complete response and/or partial response) was evaluated using World Health Organization (WHO) criteria by clinical examination and by mammography and breast echography with bi-dimensional measurements at Week 6. As per WHO criteria: complete response is defined as the disappearance of all lesions; partial response is defined as a greater than 50% decrease in the sum of products of the greatest length and width of the largest lesion; progressive disease is defined as a greater than 25% increase in the sum of products of all measurable lesions. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Week 6  |  |

| End point values            | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|-----------------------------|---|-------------------|---------------------|--|
| Subject group type          | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed | 152   | 154               | 149                 |  |
| Units: participants         |   |                   |                     |  |
| Overall Response            | 102   | 81                | 45                  |  |
| No Change                   | 33  | 57                | 81                  |  |
| Progressive Disease         | 2   | 5                 | 11                  |  |
| Not Evaluated               | 12  | 7                 | 9                   |  |
| Missing Data                | 3   | 4                 | 3                   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall response at the time of surgery

|  |   |
|--|---|
| End point title  | Overall response at the time of surgery |
| End point description:   |   |
| The number of participants with overall response (complete response and/or partial response) was evaluated using WHO criteria by clinical examination and mammography and breast echography with bi-dimensional measurements at the time of surgery (Weeks 20 to 22). As per WHO criteria: complete response is defined as the disappearance of all lesions; partial response is defined as a greater than 50% decrease in the sum of products of the greatest length and width of the largest lesion; progressive disease is defined as a greater than 25% increase in the sum of products of all measurable lesions. |   |
| End point type   | Secondary                               |
| End point timeframe:   |   |
| Time of surgery (Weeks 20 to 22)   |   |

| End point values            | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|-----------------------------|---|-------------------|---------------------|--|
| Subject group type          | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed | 152   | 154               | 149                 |  |
| Units: participants         |   |                   |                     |  |
| Overall Response            | 122   | 114               | 105                 |  |
| No Change                   | 7   | 8                 | 16                  |  |
| Progressive Disease         | 1   | 0                 | 2                   |  |
| Not Evaluated               | 14  | 19                | 20                  |  |
| Missing Data                | 8   | 13                | 6                   |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Number of participants with negative lymph nodes at the time of surgery**

|                 |   |
|-----------------|---|
| End point title | Number of participants with negative lymph nodes at the time of surgery |
|-----------------|---|

End point description:

Participants were assessed for node-negative lymph nodes at the time of surgery. As per the pathological TNM (Tumor, Node, Metastases) classification (pTNM) of malignant tumors: pN, absence or presence and extent of regional lymph node metastasis. Node-negative (pN0) participants had no regional lymph node metastasis. Although not assessed in this measure, pT is the extent of primary tumor, and pM is the absence or presence of distant metastasis.

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

End point timeframe:

Time of surgery (Weeks 20 to 22)

| End point values            | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|-----------------------------|---|-------------------|---------------------|--|
| Subject group type          | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed | 137   | 139               | 140                 |  |
| Units: participants         | 100   | 72                | 82                  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of participants with actual indicated surgery**

|                 |  |
|-----------------|--|
| End point title | Number of participants with actual indicated surgery |
|-----------------|--|

End point description:

Participants were assessed for the type of surgery they underwent for breast cancer. Non-conservative surgery is defined as a radical or modified radical mastectomy. Conservative surgery is comprised of a lumpectomy, a quadrantectomy/segmentectomy, or a partial mastectomy. Participants who were not assessed as being candidates for non-conservative or conservative surgery were classified as non-operable.

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

End point timeframe:

At surgery (Weeks 20 to 22)

| End point values            | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|-----------------------------|---|-------------------|---------------------|--|
| Subject group type          | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed | 152   | 154               | 149                 |  |
| Units: participants         |   |                   |                     |  |
| Conservative                | 63  | 66                | 58                  |  |
| Non-conservative            | 80  | 77                | 85                  |  |
| Non-operable                | 9   | 11                | 6                   |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change from baseline in tumor size at Week 6 and at surgery

|                 |  |
|-----------------|--|
| End point title | Mean change from baseline in tumor size at Week 6 and at surgery |
|-----------------|--|

End point description:

Mean change from baseline in tumor in tumor size. Change from baseline in tumor size was defined as tumor size at Week 6/ surgery (Weeks 20 to 22) minus tumor size at baseline. The difference in treatment arms was estimated for Lapatinib 1500 mg versus Trastuzumab 2 mg/kg and for Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg versus Trastuzumab 2 mg/kg.

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

End point timeframe:

Week 6 and surgery (Weeks 20 to 22)

| End point values                     | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|--------------------------------------|---|-------------------|---------------------|--|
| Subject group type                   | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed          | 152   | 154               | 149                 |  |
| Units: millimeters                   |   |                   |                     |  |
| arithmetic mean (standard deviation) |   |                   |                     |  |
| Week 6                               | -25.77 (± 19.91)                            | -20.45 (± 18.43)  | -13.42 (± 16.44)    |  |
| Surgery (Weeks 20 to 22)             | -43.59 (± 26.88)                            | -41.01 (± 23.81)  | -35.47 (± 22.95)    |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants starting paclitaxel before completing 6 weeks of treatment with either lapatinib or trastuzumab

|                 |  |
|-----------------|--|
| End point title | Number of participants starting paclitaxel before completing 6 weeks of treatment with either lapatinib or trastuzumab |
|-----------------|--|

End point description:

Participants with progressive disease at 4 week assessment that were permitted to commence treatment with paclitaxel.

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

End point timeframe:

Week 6



| End point values            | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|-----------------------------|---|-------------------|---------------------|--|
| Subject group type          | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed | 149   | 149               | 146                 |  |
| Units: participants         | 6   | 8                 | 12                  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Event-free Survival (EFS) - Median clinical follow-up

|  |   |
|--|---|
| End point title  | Event-free Survival (EFS) - Median clinical follow-up |
| End point description:   |   |
| Event free survival (EFS) is defined as the time from randomization to first EFS event. For subjects who had breast cancer surgery, EFS events were post-surgery breast cancer relapse, second primary malignancy or death without recurrence. For subjects who did not have breast cancer surgery, EFS events were death during clinical follow-up or non-completion of any neoadjuvant investigational product due to disease progression. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From randomization up to approximately year 10   |   |

| End point values                 | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg   | Trastuzumab 2 mg/kg |  |
|----------------------------------|---|---------------------|---------------------|--|
| Subject group type               | Reporting group                             | Reporting group     | Reporting group     |  |
| Number of subjects analysed      | 152   | 154                 | 149                 |  |
| Units: years                     |   |                     |                     |  |
| median (confidence interval 95%) | 9.69 (9.55 to 9.73)                         | 9.60 (8.21 to 9.69) | 9.66 (9.50 to 9.72) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Event-free Survival (EFS) - Events and censoring

|   |  |
|---|--|
| End point title   | Event-free Survival (EFS) - Events and censoring |
| End point description:  |  |
| Event free survival (EFS) is defined as the time from randomization to first EFS event. For subjects who had breast cancer surgery, EFS events were post-surgery breast cancer relapse, second primary malignancy or death without recurrence. For subjects who did not have breast cancer surgery, EFS |  |

events were death during clinical follow-up or non-completion of any neoadjuvant investigational product due to disease progression.

|  |           |
|--|-----------|
| End point type                                 | Secondary |
| End point timeframe:                           |           |
| From randomization up to approximately year 10 |           |

| End point values                                 | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|--|---|-------------------|---------------------|--|
| Subject group type                               | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed                      | 152   | 154               | 149                 |  |
| Units: Number of Participants                    |   |                   |                     |  |
| Number of subjects with EFS events               | 43  | 47                | 47                  |  |
| Number of subjects censored - total              | 109   | 107               | 102                 |  |
| Number of pts censored - Clinical f-up ongoing   | 0   | 0                 | 0                   |  |
| Number of pts censored - f-up ended - total      | 103   | 105               | 99                  |  |
| Number of pts censored - Completed f-up          | 61  | 49                | 58                  |  |
| Number of pts censored - Lost to f-up            | 17  | 20                | 10                  |  |
| Number of pts censored - W/d but consent for f/u | 3   | 6                 | 4                   |  |
| Number of pts censored - f-up ended - Withdrew   | 22  | 30                | 27                  |  |
| Number of subjects censored - Other              | 6   | 2                 | 3                   |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | EFS   |
| Comparison groups                       | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg v Trastuzumab 2 mg/kg |
| Number of subjects included in analysis | 301   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           |   |
| P-value                                 | = 0.548 <sup>[1]</sup>  |
| Method                                  | Regression, Cox   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.878   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.57  |
| upper limit                             | 1.34  |

Notes:

[1] - The two-sided stratified log-rank test was implemented as the score test from the Cox model.

|                            |     |
|----------------------------|-----|
| Statistical analysis title | EFS |
|----------------------------|-----|

|   |   |
|---|---|
| Comparison groups                       | Lapatinib 1500 mg v Trastuzumab 2 mg/kg |
| Number of subjects included in analysis | 303                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           |   |
| P-value                                 | = 0.981 <sup>[2]</sup>                  |
| Method                                  | Regression, Cox                         |
| Parameter estimate                      | Hazard ratio (HR)                       |
| Point estimate                          | 1.005                                   |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | 0.66                                    |
| upper limit                             | 1.52                                    |

Notes:

[2] - The two-sided stratified log-rank test was implemented as the score test from the Cox model.

### Secondary: Overall Survival (OS) - Median survival follow-up

|                        |  |
|------------------------|--|
| End point title        | Overall Survival (OS) - Median survival follow-up  |
| End point description: | Overall survival is defined as the period from randomization until death (from any cause). OS was assessed annually for up to 10 years after the randomization of the last participant into the study. |
| End point type         | Secondary  |
| End point timeframe:   | From randomization up to approximately year 10   |

| End point values                 | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg   | Trastuzumab 2 mg/kg |  |
|----------------------------------|---|---------------------|---------------------|--|
| Subject group type               | Reporting group                             | Reporting group     | Reporting group     |  |
| Number of subjects analysed      | 152   | 154                 | 149                 |  |
| Units: years                     |   |                     |                     |  |
| median (confidence interval 95%) | 9.70 (9.60 to 9.76)                         | 9.62 (8.86 to 9.67) | 9.64 (9.35 to 9.71) |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS) - Deaths and censoring

|                        |  |
|------------------------|--|
| End point title        | Overall Survival (OS) - Deaths and censoring   |
| End point description: | Overall survival is defined as the period from randomization until death (from any cause). OS was assessed annually for up to 10 years after the randomization of the last participant into the study. |
| End point type         | Secondary  |
| End point timeframe:   | From randomization up to approximately year 10   |

| <b>End point values</b>                               | Lapatinib<br>1000/750 mg<br>+ Trastuzumab<br>2 mg/kg | Lapatinib 1500<br>mg | Trastuzumab 2<br>mg/kg |  |
|---|--|----------------------|------------------------|--|
| Subject group type                                    | Reporting group                                      | Reporting group      | Reporting group        |  |
| Number of subjects analysed                           | 152  | 154                  | 149                    |  |
| Units: Number of Participants                         |  |                      |                        |  |
| Number of deaths due to any cause                     | 26   | 31                   | 32                     |  |
| Number of subjects censored - total                   | 126  | 123                  | 117                    |  |
| Number of pts censored - Survival f-up<br>ongoing     | 0  | 0                    | 0                      |  |
| Number of pts censored - f-up ended -<br>total        | 120  | 121                  | 114                    |  |
| Number of pts censored - Completed f-<br>up           | 74   | 59                   | 62                     |  |
| Number of pts censored - f-up ended -<br>Lost to f-up | 22   | 27                   | 18                     |  |
| Number of pts censored - f-up ended -<br>Withdrew     | 24   | 35                   | 34                     |  |
| Number of subjects censored - Other                   | 6  | 2                    | 3                      |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | OS   |
| Comparison groups                       | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg v<br>Trastuzumab 2 mg/kg |
| Number of subjects included in analysis | 301  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.379 <sup>[3]</sup>   |
| Method                                  | Regression, Cox  |
| Parameter estimate                      | Hazard ratio (HR)  |
| Point estimate                          | 0.788  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 0.46   |
| upper limit                             | 1.34   |

Notes:

[3] - The two-sided stratified log-rank test was implemented as the score test from the Cox model.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | OS                                      |
| Comparison groups                 | Lapatinib 1500 mg v Trastuzumab 2 mg/kg |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 303                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           |                       |
| P-value                                 | = 0.88 <sup>[4]</sup> |
| Method                                  | Regression, Cox       |
| Parameter estimate                      | Hazard ratio (HR)     |
| Point estimate                          | 0.962                 |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.58                  |
| upper limit                             | 1.6                   |

Notes:

[4] - The two-sided stratified log-rank test was implemented as the score test from the Cox model.

---

### Secondary: Assess associations between locoregional pathological Complete Response (pCR) and Event-free Survival (EFS) - Median clinical follow-up (EFS landmark population)

|                 |   |
|-----------------|---|
| End point title | Assess associations between locoregional pathological Complete Response (pCR) and Event-free Survival (EFS) - Median clinical follow-up (EFS landmark population) |
|-----------------|---|

End point description:

The landmark date is 30 weeks after a subject's randomization. Subjects with missing pCR status were not included in the landmark analysis. For EFS, the landmark population was the subset of the ITT population who have not had an EFS event within 30 weeks after randomization and were still in clinical follow-up.

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

End point timeframe:

up to year 10

| End point values                   | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg   | Trastuzumab 2 mg/kg | Intent to treat      |
|------------------------------------|---|---------------------|---------------------|----------------------|
| Subject group type                 | Reporting group                             | Reporting group     | Reporting group     | Subject analysis set |
| Number of subjects analysed        | 138   | 134                 | 138                 | 410                  |
| Units: years                       |   |                     |                     |                      |
| median (confidence interval 95%)   |   |                     |                     |                      |
| Median clinical follow-up - pCR    | 9.13 (8.97 to 9.23)                         | 8.08 (6.08 to 9.12) | 8.98 (8.38 to 9.21) | 9.05 (8.86 to 9.14)  |
| Median clinical follow-up - No pCR | 9.10 (7.24 to 9.15)                         | 9.09 (8.52 to 9.19) | 9.12 (9.03 to 9.25) | 9.11 (9.05 to 9.14)  |
| Overall                            | 9.12 (8.97 to 9.15)                         | 9.05 (8.23 to 9.12) | 9.11 (8.96 to 9.17) | 9.09 (9.03 to 9.13)  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Assess associations between locoregional pathological Complete Response (pCR) and Event-free Survival (EFS) - Number of participants with EFS events (EFS landmark population)**

---

|                 |  |
|-----------------|--|
| End point title | Assess associations between locoregional pathological Complete Response (pCR) and Event-free Survival (EFS) - Number of participants with EFS events (EFS landmark population) |
|-----------------|--|

**End point description:**

The landmark date is 30 weeks after a subject's randomization. Subjects with missing pCR status were not included in the landmark analysis. For EFS, the landmark population was the subset of the ITT population who have not had an EFS event within 30 weeks after randomization and were still in clinical follow-up.

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

**End point timeframe:**

up to year 10

---

| End point values                                | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg | Intent to treat      |
|---|---|-------------------|---------------------|----------------------|
| Subject group type                              | Reporting group                             | Reporting group   | Reporting group     | Subject analysis set |
| Number of subjects analysed                     | 138   | 134               | 138                 | 410                  |
| Units: Number of participants                   |   |                   |                     |                      |
| Number of participants with EFS events - pCR    | 11  | 7                 | 11                  | 29                   |
| Number of participants with EFS events - No pCR | 28  | 36                | 34                  | 98                   |
| Overall   | 39  | 43                | 45                  | 127                  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Assess associations between locoregional pathological Complete Response (pCR) and Event-free Survival (EFS) - Estimate of hazard ratio of pCR vs. no pCR (EFS landmark population)**

---

|                 |  |
|-----------------|--|
| End point title | Assess associations between locoregional pathological Complete Response (pCR) and Event-free Survival (EFS) - Estimate of hazard ratio of pCR vs. no pCR (EFS landmark population) |
|-----------------|--|

**End point description:**

This reports the estimate of the hazard ratio of pCR vs. no pCR. The landmark date is 30 weeks after a subject's randomization. Subjects with missing pCR status were not included in the landmark analysis. For EFS, the landmark population was the subset of the ITT population who have not had an EFS event within 30 weeks after randomization and were still in clinical follow-up.

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

**End point timeframe:**

up to year 10

---

| End point values                 | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg    | Trastuzumab 2 mg/kg  | Intent to treat      |
|----------------------------------|---|----------------------|----------------------|----------------------|
| Subject group type               | Reporting group                             | Reporting group      | Reporting group      | Subject analysis set |
| Number of subjects analysed      | 138 <sup>[5]</sup>                          | 134 <sup>[6]</sup>   | 138 <sup>[7]</sup>   | 410 <sup>[8]</sup>   |
| Units: Estimate of hazard ratio  |   |                      |                      |                      |
| number (confidence interval 95%) | 0.350 (0.16 to 0.71)                        | 0.532 (0.21 to 1.16) | 0.601 (0.28 to 1.20) | 0.481 (0.31 to 0.73) |

Notes:

[5] - Estimate of hazard ratio of pCR vs.no pCR

[6] - Estimate of hazard ratio of pCR vs. no pCR

[7] - Estimate of hazard ratio of pCR vs.no pCR

[8] - Estimate of hazard ratio of pCR vs.no pCR

## Statistical analyses

No statistical analyses for this end point

## Secondary: Assess associations between locoregional pathological Complete Response (pCR) and and Overall Survival (OS) - Median clinical follow-up (OS landmark population)

|                 |  |
|-----------------|--|
| End point title | Assess associations between locoregional pathological Complete Response (pCR) and and Overall Survival (OS) - Median clinical follow-up (OS landmark population) |
|-----------------|--|

End point description:

The landmark date is 30 weeks after a subject's randomization. Subjects with missing pCR status were not included in the landmark analysis. For OS, the landmark population was the subset of the ITT population who were alive and were followed up for overall survival 30 weeks after randomization.

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

End point timeframe:

up to year 10

| End point values                   | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg   | Trastuzumab 2 mg/kg | Intent to treat      |
|------------------------------------|---|---------------------|---------------------|----------------------|
| Subject group type                 | Reporting group                             | Reporting group     | Reporting group     | Subject analysis set |
| Number of subjects analysed        | 139   | 139                 | 142                 | 420                  |
| Units: years                       |   |                     |                     |                      |
| median (confidence interval 95%)   |   |                     |                     |                      |
| Median clinical follow-up - pCR    | 9.14 (9.05 to 9.24)                         | 8.31 (7.24 to 9.15) | 8.98 (8.02 to 9.21) | 9.10 (8.97 to 9.18)  |
| Median clinical follow-up - No pCR | 9.09 (7.95 to 9.15)                         | 9.08 (8.95 to 9.14) | 9.09 (8.51 to 9.15) | 9.09 (9.03 to 9.12)  |
| Overall                            | 9.12 (9.05 to 9.16)                         | 9.07 (8.50 to 9.12) | 9.07 (8.86 to 9.14) | 9.09 (9.04 to 9.13)  |

## Statistical analyses

**Secondary: Assess associations between locoregional pathological Complete Response (pCR) and Overall Survival (OS) - Number of participants with OS events (OS landmark population)**

|                 |  |
|-----------------|--|
| End point title | Assess associations between locoregional pathological Complete Response (pCR) and Overall Survival (OS) - Number of participants with OS events (OS landmark population) |
|-----------------|--|

## End point description:

The landmark date is 30 weeks after a subject's randomization. Subjects with missing pCR status were not included in the landmark analysis. For OS, the landmark population was the subset of the ITT population who were alive and were followed up for overall survival 30 weeks after randomization.

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

## End point timeframe:

up to year 10

| End point values                         | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg | Intent to treat      |
|--|---|-------------------|---------------------|----------------------|
| Subject group type                       | Reporting group                             | Reporting group   | Reporting group     | Subject analysis set |
| Number of subjects analysed              | 139   | 139               | 142                 | 420                  |
| Units: Number of Participants            |   |                   |                     |                      |
| Number of participants who died - pCR    | 5   | 4                 | 6                   | 15                   |
| Number of participants who died - No pCR | 19  | 26                | 25                  | 70                   |
| Overall                                  | 24  | 30                | 31                  | 85                   |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Assess associations between locoregional pathological Complete Response (pCR) and Overall Survival (OS) - Estimate of hazard ratio of pCR vs. no pCR (OS landmark population)**

|                 |   |
|-----------------|---|
| End point title | Assess associations between locoregional pathological Complete Response (pCR) and Overall Survival (OS) - Estimate of hazard ratio of pCR vs. no pCR (OS landmark population) |
|-----------------|---|

## End point description:

This reports the estimate of the hazard ratio of pCR vs. no pCR. The landmark date is 30 weeks after a subject's randomization. Subjects with missing pCR status were not included in the landmark analysis. For OS, the landmark population was the subset of the ITT population who were alive and were followed up for overall survival 30 weeks after randomization.

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

## End point timeframe:

up to year 10



| End point values                 | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg    | Trastuzumab 2 mg/kg  | Intent to treat      |
|----------------------------------|---|----------------------|----------------------|----------------------|
| Subject group type               | Reporting group                             | Reporting group      | Reporting group      | Subject analysis set |
| Number of subjects analysed      | 139 <sup>[9]</sup>                          | 139 <sup>[10]</sup>  | 142 <sup>[11]</sup>  | 420 <sup>[12]</sup>  |
| Units: Estimate of hazard ratio  |   |                      |                      |                      |
| number (confidence interval 95%) | 0.223 (0.07 to 0.58)                        | 0.433 (0.12 to 1.17) | 0.414 (0.15 to 1.00) | 0.366 (0.20 to 0.63) |

Notes:

[9] - Estimate of hazard ratio of pCR vs.no pCR

[10] - Estimate of hazard ratio of pCR vs.no pCR

[11] - Estimate of hazard ratio of pCR vs.no pCR

[12] - Estimate of hazard ratio of pCR vs.no pCR

## Statistical analyses

No statistical analyses for this end point

## Secondary: To assess safety via a comparison of the three treatment arms - to measure on-treatment primary cardiac endpoints

|                 |   |
|-----------------|---|
| End point title | To assess safety via a comparison of the three treatment arms - to measure on-treatment primary cardiac endpoints |
|-----------------|---|

End point description:

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

End point timeframe:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 31 weeks.

| End point values            | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|-----------------------------|---|-------------------|---------------------|--|
| Subject group type          | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed | 149   | 151               | 148                 |  |
| Units: Participants         | 2   | 0                 | 1                   |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Metabolic Response of Complete Response (mCR), Partial Response (mPR), or Stable Disease (mSD) as Determined by Positron Emission Tomography/Computed Tomography (PET/CT)

|                 |   |
|-----------------|---|
| End point title | Number of Participants With Metabolic Response of Complete Response (mCR), Partial Response (mPR), or Stable Disease (mSD) as Determined by Positron Emission Tomography/Computed Tomography (PET/CT) |
|-----------------|---|

End point description:

European Organisation for Research and Treatment of Cancer recommendations were used to define

metabolic response. mCR, complete metabolic response: complete resolution of fludeoxyglucose uptake within tumor, indistinguishable from surrounding normal tissue. mPR, partial metabolic response: reduction of more than 25% of maximum tumor standard uptake value (SUV). mSD, stable metabolic disease: increase of <25% in tumor SUV or decrease of >20% in tumor SUV. mPD, progressive metabolic disease: increase of >25% in tumor SUV or >20% in the extent (longest dimension) or appearance of new metastases.

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| Baseline, Week 2, and Week 6 |           |

| End point values              | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|-------------------------------|---|-------------------|---------------------|--|
| Subject group type            | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed   | 0 <sup>[13]</sup>                           | 0 <sup>[14]</sup> | 0 <sup>[15]</sup>   |  |
| Units: Number of Participants |   |                   |                     |  |

Notes:

[13] - This translational outcome measure was not analyzed.

[14] - This translational outcome measure was not analyzed.

[15] - This translational outcome measure was not analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With the Indicated Biomarker Expression

|                 |  |
|-----------------|--|
| End point title | Number of Participants With the Indicated Biomarker Expression |
|-----------------|--|

End point description:

Biomarker levels (Ki67, p27, Cyclin-D1, ErbB1, ErbB2, ErbB3, pErbB1, pErbB2, Akt and pAkt, S6 and pS6, MAPK and pMAPK, c-myc, IGFR1, p95HER2, PTEN, ER (alpha, beta), PgR, CD34, terminal deoxynucleotidyl transferase biotin-dUTP nick and labelling technique [TUNEL] and topoisomerase II) were assessed in participants. Blood and tumor tissue samples were collected at Baseline and at Weeks 2 and 20-22; however, data for this outcome measure cannot be presented at this time as they have yet to be evaluated and reviewed.

|   |           |
|---|-----------|
| End point type                                    | Secondary |
| End point timeframe:                              |           |
| Baseline, Week 2, and at surgery (Weeks 20 to 22) |           |

| End point values              | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|-------------------------------|---|-------------------|---------------------|--|
| Subject group type            | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed   | 0 <sup>[16]</sup>                           | 0 <sup>[17]</sup> | 0 <sup>[18]</sup>   |  |
| Units: Number of Participants |   |                   |                     |  |

Notes:

[16] - This translational outcome measure was not analyzed.

[17] - This translational outcome measure was not analyzed.

[18] - This translational outcome measure was not analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Circulating Tumor Cells (CTC) in the Bloodstream

|                 |  |
|-----------------|--|
| End point title | Number of Circulating Tumor Cells (CTC) in the Bloodstream |
|-----------------|--|

End point description:

Circulating tumor cells (CTCs) are cells that have detached from a primary tumor and circulate in the bloodstream. In the adjuvant phase, after surgery all participants received 3 courses of adjuvant 5-fluorouracil, epirubicin and cyclophosphamide, followed by lapatinib 1500 mg or trastuzumab 2 mg/kg or lapatinib 1000/750 mg plus trastuzumab 2 mg/kg given prior to surgery in the neoadjuvant setting for an additional 34 weeks. Data for this outcome measure cannot be presented at this time as they have yet to be evaluated and reviewed.

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

End point timeframe:

Baseline, Week 2 of neo-adjuvant phase (Weeks 1-34), at surgery (Weeks 20 to 22), Week 10 of adjuvant phase, 6 months after completion of adjuvant treatment, and at recurrence

| End point values                         | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Lapatinib 1500 mg | Trastuzumab 2 mg/kg |  |
|--|---|-------------------|---------------------|--|
| Subject group type                       | Reporting group                             | Reporting group   | Reporting group     |  |
| Number of subjects analysed              | 0 <sup>[19]</sup>                           | 0 <sup>[20]</sup> | 0 <sup>[21]</sup>   |  |
| Units: Number of Circulating Tumor Cells |   |                   |                     |  |

Notes:

[19] - This translational outcome measure was not analyzed.

[20] - This translational outcome measure was not analyzed.

[21] - This translational outcome measure was not analyzed.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 31 weeks.

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 | 23.0 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg |
|-----------------------|---|

Reporting group description:

Lap+Tras

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Trastuzumab 2 mg/kg |
|-----------------------|---------------------|

Reporting group description:

Tras

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Lapatinib 1500 mg |
|-----------------------|-------------------|

Reporting group description:

Lap

| Serious adverse events  | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Trastuzumab 2 mg/kg | Lapatinib 1500 mg |
|---|---|---------------------|-------------------|
| Total subjects affected by serious adverse events                   |   |                     |                   |
| subjects affected / exposed   | 61 / 149 (40.94%)                           | 36 / 148 (24.32%)   | 58 / 151 (38.41%) |
| number of deaths (all causes)                                       | 1   | 0                   | 2                 |
| number of deaths resulting from adverse events                      | 0   | 0                   | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |                     |                   |
| LOBULAR BREAST CARCINOMA IN SITU                                    |   |                     |                   |
| subjects affected / exposed   | 0 / 149 (0.00%)                             | 0 / 148 (0.00%)     | 1 / 151 (0.66%)   |
| occurrences causally related to treatment / all                     | 0 / 0                                       | 0 / 0               | 0 / 1             |
| deaths causally related to treatment / all                          | 0 / 0                                       | 0 / 0               | 0 / 0             |
| UTERINE LEIOMYOMA   |   |                     |                   |
| subjects affected / exposed   | 1 / 149 (0.67%)                             | 0 / 148 (0.00%)     | 0 / 151 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 1                                       | 0 / 0               | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0                                       | 0 / 0               | 0 / 0             |
| Vascular disorders  |   |                     |                   |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| JUGULAR VEIN THROMBOSIS                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 149 (0.00%) | 1 / 148 (0.68%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| ASTHENIA   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| CHEST DISCOMFORT                                     |                 |                 |                 |
| subjects affected / exposed                          | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| CHEST PAIN   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| GENERAL PHYSICAL HEALTH DETERIORATION                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| PYREXIA  |                 |                 |                 |
| subjects affected / exposed                          | 5 / 149 (3.36%) | 2 / 148 (1.35%) | 2 / 151 (1.32%) |
| occurrences causally related to treatment / all      | 2 / 5           | 1 / 2           | 3 / 4           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders             |                 |                 |                 |
| METRORRHAGIA   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 149 (0.00%) | 1 / 148 (0.68%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| VULVOVAGINAL PRURITUS                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| ASTHMA  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| INTERSTITIAL LUNG DISEASE                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 149 (1.34%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| ORGANISING PNEUMONIA                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| PNEUMONITIS                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| PNEUMOTHORAX                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| PULMONARY EMBOLISM                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Injury, poisoning and procedural complications  |                 |                 |                 |
| ACCIDENTAL OVERDOSE                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| INFUSION RELATED REACTION                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 148 (0.68%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| LUMBAR VERTEBRAL FRACTURE                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| POISONING                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| SEROMA  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 1 / 148 (0.68%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| SPINAL FRACTURE                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| TOXICITY TO VARIOUS AGENTS                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| TRANSFUSION REACTION                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cardiac disorders                               |                 |                 |                 |
| CARDIAC FAILURE CONGESTIVE                      |                 |                 |                 |
| subjects affected / exposed                     | 3 / 149 (2.01%) | 1 / 148 (0.68%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| CARDIO-RESPIRATORY ARREST                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| MYOCARDIAL INFARCTION                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| HEADACHE  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 148 (0.68%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| NEUROPATHY PERIPHERAL                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| SCIATICA  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| AGRANULOCYTOSIS                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| ANAEMIA   |                 |                 |                 |



|   |                  |                   |                  |
|---|------------------|-------------------|------------------|
| subjects affected / exposed                     | 0 / 149 (0.00%)  | 0 / 148 (0.00%)   | 1 / 151 (0.66%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0             | 1 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| <b>FEBRILE NEUTROPENIA</b>                      |                  |                   |                  |
| subjects affected / exposed                     | 3 / 149 (2.01%)  | 8 / 148 (5.41%)   | 2 / 151 (1.32%)  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 9             | 1 / 2            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| <b>LEUKOPENIA</b>                               |                  |                   |                  |
| subjects affected / exposed                     | 2 / 149 (1.34%)  | 1 / 148 (0.68%)   | 0 / 151 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 1             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| <b>NEUTROPENIA</b>                              |                  |                   |                  |
| subjects affected / exposed                     | 14 / 149 (9.40%) | 16 / 148 (10.81%) | 13 / 151 (8.61%) |
| occurrences causally related to treatment / all | 5 / 20           | 2 / 19            | 2 / 15           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| <b>PANCYTOPENIA</b>                             |                  |                   |                  |
| subjects affected / exposed                     | 1 / 149 (0.67%)  | 0 / 148 (0.00%)   | 0 / 151 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| <b>Gastrointestinal disorders</b>               |                  |                   |                  |
| <b>DIARRHOEA</b>                                |                  |                   |                  |
| subjects affected / exposed                     | 9 / 149 (6.04%)  | 0 / 148 (0.00%)   | 9 / 151 (5.96%)  |
| occurrences causally related to treatment / all | 11 / 11          | 0 / 0             | 9 / 9            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| <b>DUODENITIS</b>                               |                  |                   |                  |
| subjects affected / exposed                     | 1 / 149 (0.67%)  | 0 / 148 (0.00%)   | 0 / 151 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| <b>ENTERITIS</b>                                |                  |                   |                  |
| subjects affected / exposed                     | 1 / 149 (0.67%)  | 0 / 148 (0.00%)   | 0 / 151 (0.00%)  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             | 0 / 0            |
| <b>GASTRITIS EROSIVE</b>                        |                  |                   |                  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| GASTROINTESTINAL HAEMORRHAGE                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| INGUINAL HERNIA                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 148 (0.68%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| NAUSEA  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 149 (1.34%) | 1 / 148 (0.68%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| PANCREATITIS                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| VOMITING  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 149 (2.01%) | 2 / 148 (1.35%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| CHOLECYSTITIS ACUTE                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| HEPATITIS ACUTE                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| HYPERBILIRUBINAEMIA                             |                 |                 |                 |

|  |                   |                 |                   |
|--|-------------------|-----------------|-------------------|
| subjects affected / exposed                            | 4 / 149 (2.68%)   | 0 / 148 (0.00%) | 4 / 151 (2.65%)   |
| occurrences causally related to treatment / all        | 4 / 4             | 0 / 0           | 4 / 4             |
| deaths causally related to treatment / all             | 0 / 0             | 0 / 0           | 0 / 0             |
| <b>HYPERTRANSAMINASAEMIA</b>                           |                   |                 |                   |
| subjects affected / exposed                            | 15 / 149 (10.07%) | 3 / 148 (2.03%) | 23 / 151 (15.23%) |
| occurrences causally related to treatment / all        | 15 / 17           | 3 / 3           | 25 / 28           |
| deaths causally related to treatment / all             | 0 / 0             | 0 / 0           | 0 / 0             |
| <b>Skin and subcutaneous tissue disorders</b>          |                   |                 |                   |
| <b>BLISTER</b>   |                   |                 |                   |
| subjects affected / exposed                            | 1 / 149 (0.67%)   | 0 / 148 (0.00%) | 0 / 151 (0.00%)   |
| occurrences causally related to treatment / all        | 1 / 1             | 0 / 0           | 0 / 0             |
| deaths causally related to treatment / all             | 0 / 0             | 0 / 0           | 0 / 0             |
| <b>Renal and urinary disorders</b>                     |                   |                 |                   |
| <b>ACUTE KIDNEY INJURY</b>                             |                   |                 |                   |
| subjects affected / exposed                            | 2 / 149 (1.34%)   | 0 / 148 (0.00%) | 1 / 151 (0.66%)   |
| occurrences causally related to treatment / all        | 2 / 2             | 0 / 0           | 1 / 1             |
| deaths causally related to treatment / all             | 0 / 0             | 0 / 0           | 0 / 0             |
| <b>NEPHRECTASIA</b>                                    |                   |                 |                   |
| subjects affected / exposed                            | 0 / 149 (0.00%)   | 0 / 148 (0.00%) | 1 / 151 (0.66%)   |
| occurrences causally related to treatment / all        | 0 / 0             | 0 / 0           | 0 / 1             |
| deaths causally related to treatment / all             | 0 / 0             | 0 / 0           | 0 / 0             |
| <b>NEPHROLITHIASIS</b>                                 |                   |                 |                   |
| subjects affected / exposed                            | 0 / 149 (0.00%)   | 0 / 148 (0.00%) | 1 / 151 (0.66%)   |
| occurrences causally related to treatment / all        | 0 / 0             | 0 / 0           | 0 / 1             |
| deaths causally related to treatment / all             | 0 / 0             | 0 / 0           | 0 / 0             |
| <b>Musculoskeletal and connective tissue disorders</b> |                   |                 |                   |
| <b>OSTEOPOROTIC FRACTURE</b>                           |                   |                 |                   |
| subjects affected / exposed                            | 1 / 149 (0.67%)   | 0 / 148 (0.00%) | 0 / 151 (0.00%)   |
| occurrences causally related to treatment / all        | 0 / 1             | 0 / 0           | 0 / 0             |
| deaths causally related to treatment / all             | 0 / 0             | 0 / 0           | 0 / 0             |
| <b>ROTATOR CUFF SYNDROME</b>                           |                   |                 |                   |
| subjects affected / exposed                            | 0 / 149 (0.00%)   | 1 / 148 (0.68%) | 0 / 151 (0.00%)   |
| occurrences causally related to treatment / all        | 0 / 0             | 0 / 1           | 0 / 0             |
| deaths causally related to treatment / all             | 0 / 0             | 0 / 0           | 0 / 0             |

|   |                                   |                                   |                                   |
|---|-----------------------------------|-----------------------------------|-----------------------------------|
| <b>Infections and infestations</b><br><b>APPENDICITIS</b><br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 0 / 149 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 148 (0.68%)<br>0 / 1<br>0 / 0 | 0 / 151 (0.00%)<br>0 / 0<br>0 / 0 |
| <b>BACTERIAL SEPSIS</b><br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                   | 0 / 149 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 148 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 151 (0.66%)<br>1 / 1<br>0 / 0 |
| <b>BREAST CELLULITIS</b><br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | 1 / 149 (0.67%)<br>0 / 1<br>0 / 0 | 1 / 148 (0.68%)<br>0 / 1<br>0 / 0 | 0 / 151 (0.00%)<br>0 / 0<br>0 / 0 |
| <b>CELLULITIS</b><br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 2 / 149 (1.34%)<br>0 / 2<br>0 / 0 | 2 / 148 (1.35%)<br>0 / 2<br>0 / 0 | 1 / 151 (0.66%)<br>0 / 1<br>0 / 0 |
| <b>CELLULITIS STAPHYLOCOCCAL</b><br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                          | 1 / 149 (0.67%)<br>0 / 1<br>0 / 0 | 0 / 148 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 151 (0.00%)<br>0 / 0<br>0 / 0 |
| <b>DEVICE RELATED INFECTION</b><br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                           | 1 / 149 (0.67%)<br>0 / 1<br>0 / 0 | 0 / 148 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 151 (0.00%)<br>0 / 0<br>0 / 0 |
| <b>DEVICE RELATED SEPSIS</b><br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                              | 0 / 149 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 148 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 151 (0.66%)<br>0 / 1<br>0 / 0 |
| <b>ERYSIPELAS</b><br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 149 (0.67%)<br>0 / 1<br>0 / 0 | 0 / 148 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 151 (0.00%)<br>0 / 0<br>0 / 0 |
| <b>HEPATITIS B</b>  |                                   |                                   |                                   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| HERPES SIMPLEX                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| HERPES ZOSTER                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 148 (0.68%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| MASTITIS  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 2 / 151 (1.32%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| PHARYNGITIS                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| PNEUMONIA                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 149 (1.34%) | 2 / 148 (1.35%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| SKIN INFECTION                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| URINARY TRACT INFECTION                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 3 / 151 (1.99%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| VASCULAR DEVICE INFECTION                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| WOUND INFECTION                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| DEHYDRATION                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 2 / 151 (1.32%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| DIABETES MELLITUS                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 148 (0.68%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| HYPERPHOSPHATASAEMIA                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| HYPOGLYCAEMIA                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 148 (0.00%) | 0 / 151 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| HYPOKALAEMIA                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 148 (0.00%) | 1 / 151 (0.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                           | Lapatinib 1000/750 mg + Trastuzumab 2 mg/kg | Trastuzumab 2 mg/kg | Lapatinib 1500 mg  |
|---|---|---------------------|--------------------|
| Total subjects affected by non-serious adverse events       |   |                     |                    |
| subjects affected / exposed                                 | 147 / 149 (98.66%)                          | 141 / 148 (95.27%)  | 148 / 151 (98.01%) |
| <b>Vascular disorders</b>                                   |   |                     |                    |
| <b>FLUSHING</b>   |   |                     |                    |
| subjects affected / exposed                                 | 1 / 149 (0.67%)                             | 6 / 148 (4.05%)     | 3 / 151 (1.99%)    |
| occurrences (all)   | 1   | 6                   | 3                  |
| <b>HAEMATOMA</b>  |   |                     |                    |
| subjects affected / exposed                                 | 3 / 149 (2.01%)                             | 1 / 148 (0.68%)     | 1 / 151 (0.66%)    |
| occurrences (all)   | 3   | 1                   | 1                  |
| <b>HOT FLUSH</b>  |   |                     |                    |
| subjects affected / exposed                                 | 22 / 149 (14.77%)                           | 21 / 148 (14.19%)   | 15 / 151 (9.93%)   |
| occurrences (all)   | 26  | 23                  | 15                 |
| <b>HYPERTENSION</b>   |   |                     |                    |
| subjects affected / exposed                                 | 5 / 149 (3.36%)                             | 8 / 148 (5.41%)     | 5 / 151 (3.31%)    |
| occurrences (all)   | 5   | 11                  | 5                  |
| <b>HYPOTENSION</b>  |   |                     |                    |
| subjects affected / exposed                                 | 8 / 149 (5.37%)                             | 2 / 148 (1.35%)     | 5 / 151 (3.31%)    |
| occurrences (all)   | 9   | 2                   | 6                  |
| <b>LYMPHOEDEMA</b>  |   |                     |                    |
| subjects affected / exposed                                 | 3 / 149 (2.01%)                             | 3 / 148 (2.03%)     | 5 / 151 (3.31%)    |
| occurrences (all)   | 3   | 3                   | 5                  |
| <b>PHLEBITIS</b>  |   |                     |                    |
| subjects affected / exposed                                 | 2 / 149 (1.34%)                             | 5 / 148 (3.38%)     | 3 / 151 (1.99%)    |
| occurrences (all)   | 2   | 5                   | 3                  |
| <b>General disorders and administration site conditions</b> |   |                     |                    |
| <b>ASTHENIA</b>   |   |                     |                    |
| subjects affected / exposed                                 | 39 / 149 (26.17%)                           | 35 / 148 (23.65%)   | 47 / 151 (31.13%)  |
| occurrences (all)   | 55  | 53                  | 71                 |
| <b>AXILLARY PAIN</b>  |   |                     |                    |
| subjects affected / exposed                                 | 5 / 149 (3.36%)                             | 3 / 148 (2.03%)     | 0 / 151 (0.00%)    |
| occurrences (all)   | 6   | 4                   | 0                  |
| <b>CHEST DISCOMFORT</b>                                     |   |                     |                    |
| subjects affected / exposed                                 | 0 / 149 (0.00%)                             | 6 / 148 (4.05%)     | 3 / 151 (1.99%)    |
| occurrences (all)   | 0   | 8                   | 3                  |
| <b>CHEST PAIN</b>   |   |                     |                    |

|                             |                   |                   |                   |
|-----------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 5 / 149 (3.36%)   | 6 / 148 (4.05%)   | 5 / 151 (3.31%)   |
| occurrences (all)           | 5                 | 6                 | 6                 |
| CHILLS                      |                   |                   |                   |
| subjects affected / exposed | 11 / 149 (7.38%)  | 6 / 148 (4.05%)   | 3 / 151 (1.99%)   |
| occurrences (all)           | 13                | 6                 | 3                 |
| FACE OEDEMA                 |                   |                   |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 4 / 148 (2.70%)   | 5 / 151 (3.31%)   |
| occurrences (all)           | 3                 | 4                 | 5                 |
| FATIGUE                     |                   |                   |                   |
| subjects affected / exposed | 52 / 149 (34.90%) | 38 / 148 (25.68%) | 45 / 151 (29.80%) |
| occurrences (all)           | 81                | 55                | 54                |
| FEELING COLD                |                   |                   |                   |
| subjects affected / exposed | 0 / 149 (0.00%)   | 3 / 148 (2.03%)   | 1 / 151 (0.66%)   |
| occurrences (all)           | 0                 | 3                 | 1                 |
| GENERALISED OEDEMA          |                   |                   |                   |
| subjects affected / exposed | 1 / 149 (0.67%)   | 3 / 148 (2.03%)   | 3 / 151 (1.99%)   |
| occurrences (all)           | 3                 | 3                 | 7                 |
| INFLUENZA LIKE ILLNESS      |                   |                   |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 2 / 148 (1.35%)   | 2 / 151 (1.32%)   |
| occurrences (all)           | 3                 | 2                 | 2                 |
| MUCOSAL DRYNESS             |                   |                   |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 2 / 148 (1.35%)   | 2 / 151 (1.32%)   |
| occurrences (all)           | 3                 | 2                 | 2                 |
| MUCOSAL EROSION             |                   |                   |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 0 / 148 (0.00%)   | 0 / 151 (0.00%)   |
| occurrences (all)           | 4                 | 0                 | 0                 |
| MUCOSAL INFLAMMATION        |                   |                   |                   |
| subjects affected / exposed | 36 / 149 (24.16%) | 22 / 148 (14.86%) | 34 / 151 (22.52%) |
| occurrences (all)           | 39                | 27                | 38                |
| OEDEMA                      |                   |                   |                   |
| subjects affected / exposed | 4 / 149 (2.68%)   | 11 / 148 (7.43%)  | 0 / 151 (0.00%)   |
| occurrences (all)           | 5                 | 13                | 0                 |
| OEDEMA PERIPHERAL           |                   |                   |                   |
| subjects affected / exposed | 8 / 149 (5.37%)   | 13 / 148 (8.78%)  | 9 / 151 (5.96%)   |
| occurrences (all)           | 10                | 14                | 12                |
| PAIN                        |                   |                   |                   |



|   |                         |                         |                         |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)  | 3 / 149 (2.01%)<br>3    | 2 / 148 (1.35%)<br>2    | 6 / 151 (3.97%)<br>7    |
| PERIPHERAL SWELLING<br>subjects affected / exposed<br>occurrences (all)                                     | 4 / 149 (2.68%)<br>5    | 3 / 148 (2.03%)<br>3    | 2 / 151 (1.32%)<br>2    |
| PYREXIA<br>subjects affected / exposed<br>occurrences (all)   | 34 / 149 (22.82%)<br>43 | 23 / 148 (15.54%)<br>28 | 23 / 151 (15.23%)<br>33 |
| Immune system disorders<br>HYPERSENSITIVITY<br>subjects affected / exposed<br>occurrences (all)             | 6 / 149 (4.03%)<br>7    | 7 / 148 (4.73%)<br>8    | 6 / 151 (3.97%)<br>6    |
| SEASONAL ALLERGY<br>subjects affected / exposed<br>occurrences (all)  | 3 / 149 (2.01%)<br>3    | 0 / 148 (0.00%)<br>0    | 1 / 151 (0.66%)<br>1    |
| Reproductive system and breast disorders<br>AMENORRHOEA<br>subjects affected / exposed<br>occurrences (all) | 6 / 149 (4.03%)<br>7    | 1 / 148 (0.68%)<br>1    | 3 / 151 (1.99%)<br>3    |
| BREAST DISCHARGE<br>subjects affected / exposed<br>occurrences (all)  | 3 / 149 (2.01%)<br>4    | 0 / 148 (0.00%)<br>0    | 0 / 151 (0.00%)<br>0    |
| BREAST PAIN<br>subjects affected / exposed<br>occurrences (all)   | 6 / 149 (4.03%)<br>6    | 15 / 148 (10.14%)<br>15 | 5 / 151 (3.31%)<br>6    |
| MENSTRUATION IRREGULAR<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 149 (0.67%)<br>1    | 3 / 148 (2.03%)<br>3    | 2 / 151 (1.32%)<br>2    |
| PELVIC PAIN<br>subjects affected / exposed<br>occurrences (all)   | 0 / 149 (0.00%)<br>0    | 4 / 148 (2.70%)<br>4    | 0 / 151 (0.00%)<br>0    |
| VULVOVAGINAL DRYNESS<br>subjects affected / exposed<br>occurrences (all)                                    | 2 / 149 (1.34%)<br>2    | 3 / 148 (2.03%)<br>3    | 2 / 151 (1.32%)<br>2    |
| VULVOVAGINAL INFLAMMATION   |                         |                         |                         |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed                     | 0 / 149 (0.00%)   | 0 / 148 (0.00%)   | 4 / 151 (2.65%)   |
| occurrences (all)                               | 0                 | 0                 | 4                 |
| VULVOVAGINAL PRURITUS                           |                   |                   |                   |
| subjects affected / exposed                     | 2 / 149 (1.34%)   | 4 / 148 (2.70%)   | 2 / 151 (1.32%)   |
| occurrences (all)                               | 2                 | 5                 | 2                 |
| Respiratory, thoracic and mediastinal disorders |                   |                   |                   |
| COUGH   |                   |                   |                   |
| subjects affected / exposed                     | 25 / 149 (16.78%) | 26 / 148 (17.57%) | 17 / 151 (11.26%) |
| occurrences (all)                               | 34                | 30                | 19                |
| DYSPHONIA                                       |                   |                   |                   |
| subjects affected / exposed                     | 1 / 149 (0.67%)   | 2 / 148 (1.35%)   | 5 / 151 (3.31%)   |
| occurrences (all)                               | 1                 | 3                 | 5                 |
| DYSPNOEA  |                   |                   |                   |
| subjects affected / exposed                     | 16 / 149 (10.74%) | 13 / 148 (8.78%)  | 11 / 151 (7.28%)  |
| occurrences (all)                               | 19                | 13                | 13                |
| DYSPNOEA EXERTIONAL                             |                   |                   |                   |
| subjects affected / exposed                     | 6 / 149 (4.03%)   | 6 / 148 (4.05%)   | 2 / 151 (1.32%)   |
| occurrences (all)                               | 6                 | 7                 | 4                 |
| EPISTAXIS                                       |                   |                   |                   |
| subjects affected / exposed                     | 37 / 149 (24.83%) | 22 / 148 (14.86%) | 30 / 151 (19.87%) |
| occurrences (all)                               | 43                | 23                | 32                |
| HAEMOPTYSIS                                     |                   |                   |                   |
| subjects affected / exposed                     | 0 / 149 (0.00%)   | 3 / 148 (2.03%)   | 0 / 151 (0.00%)   |
| occurrences (all)                               | 0                 | 4                 | 0                 |
| NASAL DRYNESS                                   |                   |                   |                   |
| subjects affected / exposed                     | 6 / 149 (4.03%)   | 2 / 148 (1.35%)   | 6 / 151 (3.97%)   |
| occurrences (all)                               | 6                 | 4                 | 6                 |
| NASAL INFLAMMATION                              |                   |                   |                   |
| subjects affected / exposed                     | 5 / 149 (3.36%)   | 1 / 148 (0.68%)   | 3 / 151 (1.99%)   |
| occurrences (all)                               | 5                 | 1                 | 3                 |
| OROPHARYNGEAL PAIN                              |                   |                   |                   |
| subjects affected / exposed                     | 16 / 149 (10.74%) | 15 / 148 (10.14%) | 20 / 151 (13.25%) |
| occurrences (all)                               | 18                | 19                | 24                |
| PRODUCTIVE COUGH                                |                   |                   |                   |

|   |                         |                         |                         |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)  | 3 / 149 (2.01%)<br>3    | 0 / 148 (0.00%)<br>0    | 0 / 151 (0.00%)<br>0    |
| RHINORRHOEA<br>subjects affected / exposed<br>occurrences (all)                                   | 13 / 149 (8.72%)<br>16  | 10 / 148 (6.76%)<br>12  | 6 / 151 (3.97%)<br>6    |
| Psychiatric disorders<br>ANXIETY<br>subjects affected / exposed<br>occurrences (all)              | 7 / 149 (4.70%)<br>7    | 11 / 148 (7.43%)<br>12  | 9 / 151 (5.96%)<br>9    |
| DEPRESSION<br>subjects affected / exposed<br>occurrences (all)                                    | 7 / 149 (4.70%)<br>7    | 9 / 148 (6.08%)<br>9    | 5 / 151 (3.31%)<br>5    |
| INSOMNIA<br>subjects affected / exposed<br>occurrences (all)                                      | 34 / 149 (22.82%)<br>39 | 24 / 148 (16.22%)<br>26 | 23 / 151 (15.23%)<br>26 |
| SLEEP DISORDER<br>subjects affected / exposed<br>occurrences (all)                                | 5 / 149 (3.36%)<br>8    | 2 / 148 (1.35%)<br>3    | 4 / 151 (2.65%)<br>4    |
| Investigations<br>EJECTION FRACTION DECREASED<br>subjects affected / exposed<br>occurrences (all) | 6 / 149 (4.03%)<br>9    | 4 / 148 (2.70%)<br>4    | 2 / 151 (1.32%)<br>2    |
| GAMMA-GLUTAMYLTRANSFERASE<br>subjects affected / exposed<br>occurrences (all)                     | 3 / 149 (2.01%)<br>4    | 0 / 148 (0.00%)<br>0    | 2 / 151 (1.32%)<br>3    |
| GAMMA-GLUTAMYLTRANSFERASE<br>INCREASED<br>subjects affected / exposed<br>occurrences (all)        | 3 / 149 (2.01%)<br>3    | 1 / 148 (0.68%)<br>1    | 7 / 151 (4.64%)<br>9    |
| NEUTROPHIL COUNT INCREASED<br>subjects affected / exposed<br>occurrences (all)                    | 3 / 149 (2.01%)<br>4    | 2 / 148 (1.35%)<br>4    | 1 / 151 (0.66%)<br>1    |
| WEIGHT DECREASED<br>subjects affected / exposed<br>occurrences (all)                              | 8 / 149 (5.37%)<br>8    | 1 / 148 (0.68%)<br>1    | 10 / 151 (6.62%)<br>11  |
| WEIGHT INCREASED  |                         |                         |                         |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 2 / 149 (1.34%)<br>2 | 3 / 148 (2.03%)<br>3 | 2 / 151 (1.32%)<br>2 |
| Injury, poisoning and procedural complications   |                      |                      |                      |
| RADIATION SKIN INJURY                            |                      |                      |                      |
| subjects affected / exposed                      | 16 / 149 (10.74%)    | 18 / 148 (12.16%)    | 11 / 151 (7.28%)     |
| occurrences (all)                                | 17                   | 19                   | 11                   |
| SEROMA   |                      |                      |                      |
| subjects affected / exposed                      | 2 / 149 (1.34%)      | 6 / 148 (4.05%)      | 0 / 151 (0.00%)      |
| occurrences (all)                                | 2                    | 6                    | 0                    |
| THERMAL BURN                                     |                      |                      |                      |
| subjects affected / exposed                      | 3 / 149 (2.01%)      | 1 / 148 (0.68%)      | 0 / 151 (0.00%)      |
| occurrences (all)                                | 3                    | 1                    | 0                    |
| WOUND COMPLICATION                               |                      |                      |                      |
| subjects affected / exposed                      | 4 / 149 (2.68%)      | 6 / 148 (4.05%)      | 4 / 151 (2.65%)      |
| occurrences (all)                                | 5                    | 6                    | 4                    |
| Cardiac disorders                                |                      |                      |                      |
| CARDIAC FAILURE CONGESTIVE                       |                      |                      |                      |
| subjects affected / exposed                      | 3 / 149 (2.01%)      | 1 / 148 (0.68%)      | 0 / 151 (0.00%)      |
| occurrences (all)                                | 4                    | 1                    | 0                    |
| LEFT VENTRICULAR DYSFUNCTION                     |                      |                      |                      |
| subjects affected / exposed                      | 4 / 149 (2.68%)      | 2 / 148 (1.35%)      | 0 / 151 (0.00%)      |
| occurrences (all)                                | 6                    | 2                    | 0                    |
| PALPITATIONS                                     |                      |                      |                      |
| subjects affected / exposed                      | 6 / 149 (4.03%)      | 3 / 148 (2.03%)      | 6 / 151 (3.97%)      |
| occurrences (all)                                | 8                    | 3                    | 6                    |
| TACHYCARDIA                                      |                      |                      |                      |
| subjects affected / exposed                      | 4 / 149 (2.68%)      | 4 / 148 (2.70%)      | 2 / 151 (1.32%)      |
| occurrences (all)                                | 4                    | 4                    | 2                    |
| Nervous system disorders                         |                      |                      |                      |
| AGEUSIA  |                      |                      |                      |
| subjects affected / exposed                      | 4 / 149 (2.68%)      | 0 / 148 (0.00%)      | 3 / 151 (1.99%)      |
| occurrences (all)                                | 7                    | 0                    | 5                    |
| DIZZINESS  |                      |                      |                      |
| subjects affected / exposed                      | 13 / 149 (8.72%)     | 15 / 148 (10.14%)    | 13 / 151 (8.61%)     |
| occurrences (all)                                | 13                   | 19                   | 17                   |
| DYSGEUSIA  |                      |                      |                      |

|                                      |                   |                   |                   |
|--------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed          | 6 / 149 (4.03%)   | 1 / 148 (0.68%)   | 6 / 151 (3.97%)   |
| occurrences (all)                    | 10                | 1                 | 6                 |
| HEADACHE                             |                   |                   |                   |
| subjects affected / exposed          | 31 / 149 (20.81%) | 26 / 148 (17.57%) | 27 / 151 (17.88%) |
| occurrences (all)                    | 43                | 33                | 31                |
| HYPOAESTHESIA                        |                   |                   |                   |
| subjects affected / exposed          | 9 / 149 (6.04%)   | 12 / 148 (8.11%)  | 7 / 151 (4.64%)   |
| occurrences (all)                    | 11                | 14                | 7                 |
| MEMORY IMPAIRMENT                    |                   |                   |                   |
| subjects affected / exposed          | 2 / 149 (1.34%)   | 2 / 148 (1.35%)   | 4 / 151 (2.65%)   |
| occurrences (all)                    | 2                 | 4                 | 4                 |
| NEUROPATHY PERIPHERAL                |                   |                   |                   |
| subjects affected / exposed          | 19 / 149 (12.75%) | 19 / 148 (12.84%) | 21 / 151 (13.91%) |
| occurrences (all)                    | 22                | 21                | 22                |
| NEUROTOXICITY                        |                   |                   |                   |
| subjects affected / exposed          | 3 / 149 (2.01%)   | 3 / 148 (2.03%)   | 6 / 151 (3.97%)   |
| occurrences (all)                    | 5                 | 3                 | 6                 |
| PARAESTHESIA                         |                   |                   |                   |
| subjects affected / exposed          | 24 / 149 (16.11%) | 22 / 148 (14.86%) | 15 / 151 (9.93%)  |
| occurrences (all)                    | 25                | 26                | 16                |
| PERIPHERAL SENSORY NEUROPATHY        |                   |                   |                   |
| subjects affected / exposed          | 13 / 149 (8.72%)  | 14 / 148 (9.46%)  | 19 / 151 (12.58%) |
| occurrences (all)                    | 15                | 15                | 22                |
| POLYNEUROPATHY                       |                   |                   |                   |
| subjects affected / exposed          | 5 / 149 (3.36%)   | 3 / 148 (2.03%)   | 1 / 151 (0.66%)   |
| occurrences (all)                    | 7                 | 3                 | 2                 |
| TASTE DISORDER                       |                   |                   |                   |
| subjects affected / exposed          | 9 / 149 (6.04%)   | 1 / 148 (0.68%)   | 6 / 151 (3.97%)   |
| occurrences (all)                    | 9                 | 1                 | 8                 |
| Blood and lymphatic system disorders |                   |                   |                   |
| ANAEMIA                              |                   |                   |                   |
| subjects affected / exposed          | 36 / 149 (24.16%) | 27 / 148 (18.24%) | 33 / 151 (21.85%) |
| occurrences (all)                    | 44                | 35                | 47                |
| FEBRILE NEUTROPENIA                  |                   |                   |                   |
| subjects affected / exposed          | 3 / 149 (2.01%)   | 1 / 148 (0.68%)   | 0 / 151 (0.00%)   |
| occurrences (all)                    | 3                 | 1                 | 0                 |

|                             |                   |                   |                   |
|-----------------------------|-------------------|-------------------|-------------------|
| LEUKOPENIA                  |                   |                   |                   |
| subjects affected / exposed | 21 / 149 (14.09%) | 10 / 148 (6.76%)  | 18 / 151 (11.92%) |
| occurrences (all)           | 32                | 15                | 28                |
| LYMPHOPENIA                 |                   |                   |                   |
| subjects affected / exposed | 5 / 149 (3.36%)   | 6 / 148 (4.05%)   | 2 / 151 (1.32%)   |
| occurrences (all)           | 7                 | 7                 | 5                 |
| NEUTROPENIA                 |                   |                   |                   |
| subjects affected / exposed | 47 / 149 (31.54%) | 37 / 148 (25.00%) | 51 / 151 (33.77%) |
| occurrences (all)           | 66                | 48                | 91                |
| THROMBOCYTOPENIA            |                   |                   |                   |
| subjects affected / exposed | 4 / 149 (2.68%)   | 1 / 148 (0.68%)   | 2 / 151 (1.32%)   |
| occurrences (all)           | 4                 | 1                 | 2                 |
| Ear and labyrinth disorders |                   |                   |                   |
| EAR PAIN                    |                   |                   |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 1 / 148 (0.68%)   | 1 / 151 (0.66%)   |
| occurrences (all)           | 3                 | 1                 | 1                 |
| TINNITUS                    |                   |                   |                   |
| subjects affected / exposed | 6 / 149 (4.03%)   | 3 / 148 (2.03%)   | 1 / 151 (0.66%)   |
| occurrences (all)           | 6                 | 3                 | 1                 |
| VERTIGO                     |                   |                   |                   |
| subjects affected / exposed | 11 / 149 (7.38%)  | 6 / 148 (4.05%)   | 7 / 151 (4.64%)   |
| occurrences (all)           | 11                | 7                 | 8                 |
| Eye disorders               |                   |                   |                   |
| DRY EYE                     |                   |                   |                   |
| subjects affected / exposed | 4 / 149 (2.68%)   | 2 / 148 (1.35%)   | 1 / 151 (0.66%)   |
| occurrences (all)           | 5                 | 2                 | 1                 |
| LACRIMATION INCREASED       |                   |                   |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 1 / 148 (0.68%)   | 3 / 151 (1.99%)   |
| occurrences (all)           | 4                 | 1                 | 3                 |
| VISUAL IMPAIRMENT           |                   |                   |                   |
| subjects affected / exposed | 2 / 149 (1.34%)   | 3 / 148 (2.03%)   | 2 / 151 (1.32%)   |
| occurrences (all)           | 2                 | 4                 | 2                 |
| Gastrointestinal disorders  |                   |                   |                   |
| ABDOMINAL DISCOMFORT        |                   |                   |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 4 / 148 (2.70%)   | 1 / 151 (0.66%)   |
| occurrences (all)           | 3                 | 4                 | 1                 |
| ABDOMINAL DISTENSION        |                   |                   |                   |

|                             |                    |                   |                    |
|-----------------------------|--------------------|-------------------|--------------------|
| subjects affected / exposed | 10 / 149 (6.71%)   | 5 / 148 (3.38%)   | 8 / 151 (5.30%)    |
| occurrences (all)           | 12                 | 6                 | 9                  |
| ABDOMINAL PAIN              |                    |                   |                    |
| subjects affected / exposed | 21 / 149 (14.09%)  | 13 / 148 (8.78%)  | 28 / 151 (18.54%)  |
| occurrences (all)           | 28                 | 16                | 36                 |
| ABDOMINAL PAIN UPPER        |                    |                   |                    |
| subjects affected / exposed | 23 / 149 (15.44%)  | 16 / 148 (10.81%) | 27 / 151 (17.88%)  |
| occurrences (all)           | 32                 | 18                | 31                 |
| ANAL INFLAMMATION           |                    |                   |                    |
| subjects affected / exposed | 4 / 149 (2.68%)    | 1 / 148 (0.68%)   | 2 / 151 (1.32%)    |
| occurrences (all)           | 5                  | 1                 | 2                  |
| CONSTIPATION                |                    |                   |                    |
| subjects affected / exposed | 18 / 149 (12.08%)  | 15 / 148 (10.14%) | 15 / 151 (9.93%)   |
| occurrences (all)           | 23                 | 19                | 19                 |
| DIARRHOEA                   |                    |                   |                    |
| subjects affected / exposed | 128 / 149 (85.91%) | 52 / 148 (35.14%) | 123 / 151 (81.46%) |
| occurrences (all)           | 296                | 79                | 238                |
| DRY MOUTH                   |                    |                   |                    |
| subjects affected / exposed | 9 / 149 (6.04%)    | 3 / 148 (2.03%)   | 5 / 151 (3.31%)    |
| occurrences (all)           | 10                 | 3                 | 5                  |
| DYSPEPSIA                   |                    |                   |                    |
| subjects affected / exposed | 17 / 149 (11.41%)  | 10 / 148 (6.76%)  | 26 / 151 (17.22%)  |
| occurrences (all)           | 20                 | 11                | 30                 |
| DYSPHAGIA                   |                    |                   |                    |
| subjects affected / exposed | 3 / 149 (2.01%)    | 3 / 148 (2.03%)   | 0 / 151 (0.00%)    |
| occurrences (all)           | 3                  | 3                 | 0                  |
| EPIGASTRIC DISCOMFORT       |                    |                   |                    |
| subjects affected / exposed | 3 / 149 (2.01%)    | 2 / 148 (1.35%)   | 2 / 151 (1.32%)    |
| occurrences (all)           | 4                  | 2                 | 2                  |
| FLATULENCE                  |                    |                   |                    |
| subjects affected / exposed | 3 / 149 (2.01%)    | 2 / 148 (1.35%)   | 5 / 151 (3.31%)    |
| occurrences (all)           | 3                  | 2                 | 6                  |
| GASTRITIS                   |                    |                   |                    |
| subjects affected / exposed | 2 / 149 (1.34%)    | 3 / 148 (2.03%)   | 8 / 151 (5.30%)    |
| occurrences (all)           | 2                  | 3                 | 8                  |
| GASTROOESOPHAGEAL REFLUX    |                    |                   |                    |

|  |                   |                   |                   |
|--|-------------------|-------------------|-------------------|
| DISEASE                                |                   |                   |                   |
| subjects affected / exposed            | 5 / 149 (3.36%)   | 0 / 148 (0.00%)   | 2 / 151 (1.32%)   |
| occurrences (all)                      | 5                 | 0                 | 2                 |
| HAEMORRHOIDS                           |                   |                   |                   |
| subjects affected / exposed            | 13 / 149 (8.72%)  | 10 / 148 (6.76%)  | 10 / 151 (6.62%)  |
| occurrences (all)                      | 13                | 12                | 10                |
| MOUTH ULCERATION                       |                   |                   |                   |
| subjects affected / exposed            | 12 / 149 (8.05%)  | 1 / 148 (0.68%)   | 4 / 151 (2.65%)   |
| occurrences (all)                      | 16                | 1                 | 6                 |
| NAUSEA                                 |                   |                   |                   |
| subjects affected / exposed            | 75 / 149 (50.34%) | 76 / 148 (51.35%) | 81 / 151 (53.64%) |
| occurrences (all)                      | 140               | 111               | 152               |
| RECTAL HAEMORRHAGE                     |                   |                   |                   |
| subjects affected / exposed            | 4 / 149 (2.68%)   | 0 / 148 (0.00%)   | 2 / 151 (1.32%)   |
| occurrences (all)                      | 4                 | 0                 | 2                 |
| STOMATITIS                             |                   |                   |                   |
| subjects affected / exposed            | 27 / 149 (18.12%) | 23 / 148 (15.54%) | 18 / 151 (11.92%) |
| occurrences (all)                      | 39                | 25                | 29                |
| TOOTHACHE                              |                   |                   |                   |
| subjects affected / exposed            | 4 / 149 (2.68%)   | 2 / 148 (1.35%)   | 1 / 151 (0.66%)   |
| occurrences (all)                      | 4                 | 2                 | 1                 |
| VOMITING                               |                   |                   |                   |
| subjects affected / exposed            | 54 / 149 (36.24%) | 38 / 148 (25.68%) | 57 / 151 (37.75%) |
| occurrences (all)                      | 96                | 57                | 93                |
| Hepatobiliary disorders                |                   |                   |                   |
| HYPERBILIRUBINAEMIA                    |                   |                   |                   |
| subjects affected / exposed            | 21 / 149 (14.09%) | 7 / 148 (4.73%)   | 26 / 151 (17.22%) |
| occurrences (all)                      | 24                | 8                 | 33                |
| HYPERTRANSAMINASAEMIA                  |                   |                   |                   |
| subjects affected / exposed            | 55 / 149 (36.91%) | 39 / 148 (26.35%) | 55 / 151 (36.42%) |
| occurrences (all)                      | 113               | 106               | 112               |
| Skin and subcutaneous tissue disorders |                   |                   |                   |
| ACNE                                   |                   |                   |                   |
| subjects affected / exposed            | 22 / 149 (14.77%) | 5 / 148 (3.38%)   | 20 / 151 (13.25%) |
| occurrences (all)                      | 28                | 7                 | 25                |
| ALOPECIA                               |                   |                   |                   |



|                             |                   |                   |                   |
|-----------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 95 / 149 (63.76%) | 96 / 148 (64.86%) | 90 / 151 (59.60%) |
| occurrences (all)           | 101               | 103               | 97                |
| DERMATITIS                  |                   |                   |                   |
| subjects affected / exposed | 13 / 149 (8.72%)  | 8 / 148 (5.41%)   | 13 / 151 (8.61%)  |
| occurrences (all)           | 13                | 11                | 13                |
| DERMATITIS ACNEIFORM        |                   |                   |                   |
| subjects affected / exposed | 14 / 149 (9.40%)  | 4 / 148 (2.70%)   | 12 / 151 (7.95%)  |
| occurrences (all)           | 18                | 4                 | 16                |
| DRY SKIN                    |                   |                   |                   |
| subjects affected / exposed | 28 / 149 (18.79%) | 8 / 148 (5.41%)   | 29 / 151 (19.21%) |
| occurrences (all)           | 28                | 8                 | 30                |
| ECZEMA                      |                   |                   |                   |
| subjects affected / exposed | 6 / 149 (4.03%)   | 2 / 148 (1.35%)   | 4 / 151 (2.65%)   |
| occurrences (all)           | 6                 | 2                 | 4                 |
| ERYTHEMA                    |                   |                   |                   |
| subjects affected / exposed | 14 / 149 (9.40%)  | 15 / 148 (10.14%) | 14 / 151 (9.27%)  |
| occurrences (all)           | 15                | 16                | 18                |
| EXFOLIATIVE RASH            |                   |                   |                   |
| subjects affected / exposed | 8 / 149 (5.37%)   | 0 / 148 (0.00%)   | 4 / 151 (2.65%)   |
| occurrences (all)           | 9                 | 0                 | 4                 |
| HYPERHIDROSIS               |                   |                   |                   |
| subjects affected / exposed | 2 / 149 (1.34%)   | 3 / 148 (2.03%)   | 1 / 151 (0.66%)   |
| occurrences (all)           | 2                 | 3                 | 1                 |
| NAIL DISORDER               |                   |                   |                   |
| subjects affected / exposed | 36 / 149 (24.16%) | 18 / 148 (12.16%) | 26 / 151 (17.22%) |
| occurrences (all)           | 44                | 20                | 32                |
| NAIL DYSTROPHY              |                   |                   |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 1 / 148 (0.68%)   | 2 / 151 (1.32%)   |
| occurrences (all)           | 3                 | 1                 | 2                 |
| ONYCHALGIA                  |                   |                   |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 1 / 148 (0.68%)   | 3 / 151 (1.99%)   |
| occurrences (all)           | 3                 | 1                 | 3                 |
| ONYCHOLYSIS                 |                   |                   |                   |
| subjects affected / exposed | 7 / 149 (4.70%)   | 2 / 148 (1.35%)   | 0 / 151 (0.00%)   |
| occurrences (all)           | 7                 | 2                 | 0                 |
| PAIN OF SKIN                |                   |                   |                   |

|  |                   |                   |                   |
|--|-------------------|-------------------|-------------------|
| subjects affected / exposed                    | 1 / 149 (0.67%)   | 2 / 148 (1.35%)   | 4 / 151 (2.65%)   |
| occurrences (all)                              | 1                 | 2                 | 4                 |
| PALMAR-PLANTAR<br>ERYTHRODYSAESTHESIA SYNDROME |                   |                   |                   |
| subjects affected / exposed                    | 14 / 149 (9.40%)  | 3 / 148 (2.03%)   | 14 / 151 (9.27%)  |
| occurrences (all)                              | 16                | 3                 | 15                |
| PRURITUS                                       |                   |                   |                   |
| subjects affected / exposed                    | 24 / 149 (16.11%) | 9 / 148 (6.08%)   | 29 / 151 (19.21%) |
| occurrences (all)                              | 32                | 10                | 33                |
| RASH   |                   |                   |                   |
| subjects affected / exposed                    | 67 / 149 (44.97%) | 28 / 148 (18.92%) | 68 / 151 (45.03%) |
| occurrences (all)                              | 94                | 34                | 93                |
| RASH PRURITIC                                  |                   |                   |                   |
| subjects affected / exposed                    | 4 / 149 (2.68%)   | 3 / 148 (2.03%)   | 3 / 151 (1.99%)   |
| occurrences (all)                              | 4                 | 4                 | 4                 |
| SCAR PAIN                                      |                   |                   |                   |
| subjects affected / exposed                    | 1 / 149 (0.67%)   | 4 / 148 (2.70%)   | 3 / 151 (1.99%)   |
| occurrences (all)                              | 1                 | 4                 | 3                 |
| SKIN EXFOLIATION                               |                   |                   |                   |
| subjects affected / exposed                    | 4 / 149 (2.68%)   | 1 / 148 (0.68%)   | 0 / 151 (0.00%)   |
| occurrences (all)                              | 4                 | 1                 | 0                 |
| SKIN FISSURES                                  |                   |                   |                   |
| subjects affected / exposed                    | 13 / 149 (8.72%)  | 4 / 148 (2.70%)   | 4 / 151 (2.65%)   |
| occurrences (all)                              | 17                | 4                 | 5                 |
| SKIN HYPERPIGMENTATION                         |                   |                   |                   |
| subjects affected / exposed                    | 6 / 149 (4.03%)   | 2 / 148 (1.35%)   | 6 / 151 (3.97%)   |
| occurrences (all)                              | 7                 | 2                 | 6                 |
| SKIN IRRITATION                                |                   |                   |                   |
| subjects affected / exposed                    | 3 / 149 (2.01%)   | 1 / 148 (0.68%)   | 1 / 151 (0.66%)   |
| occurrences (all)                              | 3                 | 1                 | 1                 |
| SKIN LESION                                    |                   |                   |                   |
| subjects affected / exposed                    | 5 / 149 (3.36%)   | 0 / 148 (0.00%)   | 1 / 151 (0.66%)   |
| occurrences (all)                              | 6                 | 0                 | 1                 |
| SKIN REACTION                                  |                   |                   |                   |
| subjects affected / exposed                    | 2 / 149 (1.34%)   | 0 / 148 (0.00%)   | 4 / 151 (2.65%)   |
| occurrences (all)                              | 3                 | 0                 | 4                 |

|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| Renal and urinary disorders                     |                   |                   |                   |
| DYSURIA   |                   |                   |                   |
| subjects affected / exposed                     | 11 / 149 (7.38%)  | 5 / 148 (3.38%)   | 6 / 151 (3.97%)   |
| occurrences (all)                               | 12                | 6                 | 7                 |
| HAEMATURIA                                      |                   |                   |                   |
| subjects affected / exposed                     | 4 / 149 (2.68%)   | 0 / 148 (0.00%)   | 0 / 151 (0.00%)   |
| occurrences (all)                               | 4                 | 0                 | 0                 |
| Musculoskeletal and connective tissue disorders |                   |                   |                   |
| ARTHRALGIA                                      |                   |                   |                   |
| subjects affected / exposed                     | 27 / 149 (18.12%) | 32 / 148 (21.62%) | 26 / 151 (17.22%) |
| occurrences (all)                               | 31                | 38                | 31                |
| BACK PAIN                                       |                   |                   |                   |
| subjects affected / exposed                     | 22 / 149 (14.77%) | 14 / 148 (9.46%)  | 10 / 151 (6.62%)  |
| occurrences (all)                               | 25                | 15                | 11                |
| BONE PAIN                                       |                   |                   |                   |
| subjects affected / exposed                     | 10 / 149 (6.71%)  | 18 / 148 (12.16%) | 12 / 151 (7.95%)  |
| occurrences (all)                               | 13                | 21                | 12                |
| JOINT STIFFNESS                                 |                   |                   |                   |
| subjects affected / exposed                     | 2 / 149 (1.34%)   | 4 / 148 (2.70%)   | 1 / 151 (0.66%)   |
| occurrences (all)                               | 2                 | 4                 | 1                 |
| MUSCLE SPASMS                                   |                   |                   |                   |
| subjects affected / exposed                     | 6 / 149 (4.03%)   | 3 / 148 (2.03%)   | 4 / 151 (2.65%)   |
| occurrences (all)                               | 7                 | 4                 | 5                 |
| MUSCULOSKELETAL CHEST PAIN                      |                   |                   |                   |
| subjects affected / exposed                     | 4 / 149 (2.68%)   | 1 / 148 (0.68%)   | 2 / 151 (1.32%)   |
| occurrences (all)                               | 4                 | 1                 | 2                 |
| MUSCULOSKELETAL PAIN                            |                   |                   |                   |
| subjects affected / exposed                     | 8 / 149 (5.37%)   | 11 / 148 (7.43%)  | 16 / 151 (10.60%) |
| occurrences (all)                               | 9                 | 12                | 20                |
| MUSCULOSKELETAL STIFFNESS                       |                   |                   |                   |
| subjects affected / exposed                     | 1 / 149 (0.67%)   | 3 / 148 (2.03%)   | 1 / 151 (0.66%)   |
| occurrences (all)                               | 1                 | 3                 | 1                 |
| MYALGIA   |                   |                   |                   |
| subjects affected / exposed                     | 31 / 149 (20.81%) | 34 / 148 (22.97%) | 33 / 151 (21.85%) |
| occurrences (all)                               | 52                | 50                | 50                |
| NECK PAIN                                       |                   |                   |                   |

|                                   |                  |                  |                   |
|-----------------------------------|------------------|------------------|-------------------|
| subjects affected / exposed       | 7 / 149 (4.70%)  | 5 / 148 (3.38%)  | 5 / 151 (3.31%)   |
| occurrences (all)                 | 7                | 5                | 7                 |
| OSTEOPOROSIS                      |                  |                  |                   |
| subjects affected / exposed       | 0 / 149 (0.00%)  | 3 / 148 (2.03%)  | 1 / 151 (0.66%)   |
| occurrences (all)                 | 0                | 3                | 1                 |
| PAIN IN EXTREMITY                 |                  |                  |                   |
| subjects affected / exposed       | 13 / 149 (8.72%) | 13 / 148 (8.78%) | 20 / 151 (13.25%) |
| occurrences (all)                 | 18               | 16               | 25                |
| Infections and infestations       |                  |                  |                   |
| BRONCHITIS                        |                  |                  |                   |
| subjects affected / exposed       | 2 / 149 (1.34%)  | 3 / 148 (2.03%)  | 5 / 151 (3.31%)   |
| occurrences (all)                 | 2                | 3                | 6                 |
| CONJUNCTIVITIS                    |                  |                  |                   |
| subjects affected / exposed       | 11 / 149 (7.38%) | 5 / 148 (3.38%)  | 8 / 151 (5.30%)   |
| occurrences (all)                 | 13               | 5                | 8                 |
| CYSTITIS                          |                  |                  |                   |
| subjects affected / exposed       | 8 / 149 (5.37%)  | 3 / 148 (2.03%)  | 6 / 151 (3.97%)   |
| occurrences (all)                 | 8                | 3                | 6                 |
| HERPES SIMPLEX                    |                  |                  |                   |
| subjects affected / exposed       | 3 / 149 (2.01%)  | 2 / 148 (1.35%)  | 0 / 151 (0.00%)   |
| occurrences (all)                 | 3                | 2                | 0                 |
| INFLUENZA                         |                  |                  |                   |
| subjects affected / exposed       | 8 / 149 (5.37%)  | 9 / 148 (6.08%)  | 8 / 151 (5.30%)   |
| occurrences (all)                 | 9                | 10               | 8                 |
| LOCALISED INFECTION               |                  |                  |                   |
| subjects affected / exposed       | 3 / 149 (2.01%)  | 0 / 148 (0.00%)  | 3 / 151 (1.99%)   |
| occurrences (all)                 | 3                | 0                | 4                 |
| LOWER RESPIRATORY TRACT INFECTION |                  |                  |                   |
| subjects affected / exposed       | 3 / 149 (2.01%)  | 1 / 148 (0.68%)  | 1 / 151 (0.66%)   |
| occurrences (all)                 | 3                | 1                | 1                 |
| MASTITIS                          |                  |                  |                   |
| subjects affected / exposed       | 2 / 149 (1.34%)  | 3 / 148 (2.03%)  | 1 / 151 (0.66%)   |
| occurrences (all)                 | 2                | 3                | 1                 |
| NAIL INFECTION                    |                  |                  |                   |

|                                   |                   |                  |                  |
|-----------------------------------|-------------------|------------------|------------------|
| subjects affected / exposed       | 8 / 149 (5.37%)   | 0 / 148 (0.00%)  | 1 / 151 (0.66%)  |
| occurrences (all)                 | 9                 | 0                | 2                |
| NASOPHARYNGITIS                   |                   |                  |                  |
| subjects affected / exposed       | 11 / 149 (7.38%)  | 11 / 148 (7.43%) | 12 / 151 (7.95%) |
| occurrences (all)                 | 15                | 11               | 13               |
| ORAL HERPES                       |                   |                  |                  |
| subjects affected / exposed       | 2 / 149 (1.34%)   | 3 / 148 (2.03%)  | 0 / 151 (0.00%)  |
| occurrences (all)                 | 2                 | 3                | 0                |
| PARONYCHIA                        |                   |                  |                  |
| subjects affected / exposed       | 17 / 149 (11.41%) | 2 / 148 (1.35%)  | 14 / 151 (9.27%) |
| occurrences (all)                 | 22                | 2                | 22               |
| PHARYNGITIS                       |                   |                  |                  |
| subjects affected / exposed       | 4 / 149 (2.68%)   | 5 / 148 (3.38%)  | 7 / 151 (4.64%)  |
| occurrences (all)                 | 4                 | 5                | 7                |
| PUSTULE                           |                   |                  |                  |
| subjects affected / exposed       | 3 / 149 (2.01%)   | 1 / 148 (0.68%)  | 1 / 151 (0.66%)  |
| occurrences (all)                 | 3                 | 1                | 2                |
| RHINITIS                          |                   |                  |                  |
| subjects affected / exposed       | 6 / 149 (4.03%)   | 5 / 148 (3.38%)  | 4 / 151 (2.65%)  |
| occurrences (all)                 | 6                 | 5                | 4                |
| SINUSITIS                         |                   |                  |                  |
| subjects affected / exposed       | 3 / 149 (2.01%)   | 2 / 148 (1.35%)  | 5 / 151 (3.31%)  |
| occurrences (all)                 | 3                 | 2                | 5                |
| SKIN INFECTION                    |                   |                  |                  |
| subjects affected / exposed       | 4 / 149 (2.68%)   | 2 / 148 (1.35%)  | 1 / 151 (0.66%)  |
| occurrences (all)                 | 4                 | 2                | 1                |
| TONSILLITIS                       |                   |                  |                  |
| subjects affected / exposed       | 0 / 149 (0.00%)   | 4 / 148 (2.70%)  | 3 / 151 (1.99%)  |
| occurrences (all)                 | 0                 | 4                | 4                |
| UPPER RESPIRATORY TRACT INFECTION |                   |                  |                  |
| subjects affected / exposed       | 10 / 149 (6.71%)  | 14 / 148 (9.46%) | 9 / 151 (5.96%)  |
| occurrences (all)                 | 12                | 16               | 10               |
| URINARY TRACT INFECTION           |                   |                  |                  |
| subjects affected / exposed       | 11 / 149 (7.38%)  | 6 / 148 (4.05%)  | 14 / 151 (9.27%) |
| occurrences (all)                 | 11                | 6                | 16               |

|                                    |                   |                   |                   |
|------------------------------------|-------------------|-------------------|-------------------|
| VAGINAL INFECTION                  |                   |                   |                   |
| subjects affected / exposed        | 5 / 149 (3.36%)   | 2 / 148 (1.35%)   | 1 / 151 (0.66%)   |
| occurrences (all)                  | 5                 | 2                 | 1                 |
| VIRAL INFECTION                    |                   |                   |                   |
| subjects affected / exposed        | 0 / 149 (0.00%)   | 3 / 148 (2.03%)   | 0 / 151 (0.00%)   |
| occurrences (all)                  | 0                 | 3                 | 0                 |
| Metabolism and nutrition disorders |                   |                   |                   |
| DECREASED APPETITE                 |                   |                   |                   |
| subjects affected / exposed        | 35 / 149 (23.49%) | 17 / 148 (11.49%) | 39 / 151 (25.83%) |
| occurrences (all)                  | 57                | 21                | 50                |
| DEHYDRATION                        |                   |                   |                   |
| subjects affected / exposed        | 1 / 149 (0.67%)   | 0 / 148 (0.00%)   | 5 / 151 (3.31%)   |
| occurrences (all)                  | 2                 | 0                 | 6                 |
| HYPERCHOLESTEROLAEMIA              |                   |                   |                   |
| subjects affected / exposed        | 0 / 149 (0.00%)   | 3 / 148 (2.03%)   | 1 / 151 (0.66%)   |
| occurrences (all)                  | 0                 | 3                 | 1                 |
| HYPERGLYCAEMIA                     |                   |                   |                   |
| subjects affected / exposed        | 3 / 149 (2.01%)   | 4 / 148 (2.70%)   | 0 / 151 (0.00%)   |
| occurrences (all)                  | 3                 | 4                 | 0                 |
| HYPERPHOSPHATASAEMIA               |                   |                   |                   |
| subjects affected / exposed        | 22 / 149 (14.77%) | 12 / 148 (8.11%)  | 22 / 151 (14.57%) |
| occurrences (all)                  | 30                | 18                | 29                |
| HYPOKALAEMIA                       |                   |                   |                   |
| subjects affected / exposed        | 4 / 149 (2.68%)   | 0 / 148 (0.00%)   | 3 / 151 (1.99%)   |
| occurrences (all)                  | 4                 | 0                 | 3                 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment        |
|-----------------|------------------|
| 22 April 2008   | Amendment No. 01 |
| 10 October 2008 | Amendment No. 02 |
| 17 May 2013     | Amendment No. 03 |
| 13 May 2016     | Amendment No. 04 |
| 24 August 2016  | Amendment No. 05 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported