



## Clinical trial results:

### A Phase III Study for ErbB2 Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Junction Adenocarcinoma treated with Capecitabine plus Oxaliplatin with or without Lapatinib

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2007-005725-29  |
| Trial protocol           | EE IT NL HU     |
| Global end of trial date | 03 October 2024 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 23 October 2025 |
| First version publication date | 23 October 2025 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | EGF110656 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |                        |
|------------------------------------|------------------------|
| ISRCTN number                      | -                      |
| ClinicalTrials.gov id (NCT number) | NCT00680901            |
| WHO universal trial number (UTN)   | -                      |
| Other trial identifiers            | CLAP016C2301: Novartis |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | Lichtstrasse 35, Basel, Switzerland, 4056   |
| 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                       | 03 October 2024 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 03 October 2024 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

This was an international multi-center trial that enrolled patients with locally advanced, unresectable, or metastatic gastric, esophageal, or gastro-esophageal junction cancer whose tumors had amplification of the ErbB2 (HER2) gene. The trial investigated whether lapatinib, when added to the chemotherapy regimen, capecitabine plus oxaliplatin (CapeOx), extended the time to progression and overall survival. Tumor ErbB2 (HER2) status had to be known before trial entry. CapeOx was administered to all patients, and patients were randomly assigned to receive either lapatinib or placebo.

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                          | 04 June 2008 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 16          |
| Country: Number of subjects enrolled | Brazil: 29             |
| Country: Number of subjects enrolled | Canada: 6              |
| Country: Number of subjects enrolled | Chile: 17              |
| Country: Number of subjects enrolled | China: 120             |
| Country: Number of subjects enrolled | Estonia: 10            |
| Country: Number of subjects enrolled | Hong Kong: 4           |
| Country: Number of subjects enrolled | Hungary: 8             |
| Country: Number of subjects enrolled | India: 18              |
| Country: Number of subjects enrolled | Israel: 3              |
| Country: Number of subjects enrolled | Italy: 38              |
| Country: Number of subjects enrolled | Korea, Republic of: 92 |
| Country: Number of subjects enrolled | Mexico: 4              |
| Country: Number of subjects enrolled | Netherlands: 15        |
| Country: Number of subjects enrolled | Peru: 5                |
| Country: Number of subjects enrolled | Poland: 34             |
| Country: Number of subjects enrolled | Russian Federation: 62 |

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Taiwan: 4         |
| Country: Number of subjects enrolled | Türkiye: 1        |
| Country: Number of subjects enrolled | Ukraine: 48       |
| Country: Number of subjects enrolled | United States: 11 |
| Worldwide total number of subjects   | 545               |
| EEA total number of subjects         | 105               |

Notes:

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### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 368 |
| From 65 to 84 years                       | 176 |
| 85 years and over                         | 1   |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 186 centers in 21 countries in North America (Canada and US), Asia (China, Hong Kong, Korea and Taiwan), and Rest of World (ROW) (Argentina, Brazil, Chile, Estonia, Hungary, India, Israel, Italy, Mexico, Netherlands, Peru, Poland, Russian Federation, Turkey, and Ukraine).

### Pre-assignment

Screening details:

Participants were randomized into one of two treatment arms: CapeOx plus lapatinib (the experimental arm) or CapeOx plus placebo (the control arm) using a 1:1 randomization.

### Period 1

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

### Arms

|                              |                       |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes                   |
| <b>Arm title</b>             | CapeOx plus Lapatinib |

Arm description:

Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m<sup>2</sup> intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m<sup>2</sup> per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m<sup>2</sup>/day after the first cycle at the investigator's discretion. 3) Lapatinib: 1250 mg orally once daily, starting on Day 1 and continued daily throughout the cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and lapatinib were continued until disease progression, unacceptable toxicity, or withdrawal of consent.

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

Dosage and administration details:

5 pills at 250mg each once daily

|  |  |
|--|--|
| Investigational medicinal product name | Oxaliplatin  |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Concentrate for solution for infusion, Solution for infusion, Solution for injection |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

130mg/m<sup>2</sup> on day 1

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

Dosage and administration details:  
1700mg/m<sup>2</sup>/day in two daily doses

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | CapeOx plus Placebo |
|------------------|---------------------|

Arm description:

Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m<sup>2</sup> intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m<sup>2</sup> per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m<sup>2</sup>/day after the first cycle at the investigator's discretion. 3) Lapatinib matching placebo: Taken orally once daily starting on Day 1 and continued throughout each cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and the lapatinib placebo were continued until disease progression, unacceptable toxicity, or withdrawal of consent.

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Pillules |
| Routes of administration               | Oral use |

Dosage and administration details:

5 pills each once daily

|  |  |
|--|--|
| Investigational medicinal product name | Oxaliplatin  |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Concentrate for solution for infusion, Solution for infusion, Solution for injection |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

130mg/m<sup>2</sup> on day 1

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

Dosage and administration details:

1700mg/m<sup>2</sup>/day in two daily doses

| <b>Number of subjects in period 1</b> | CapeOx plus Lapatinib | CapeOx plus Placebo |
|---------------------------------------|-----------------------|---------------------|
| Started                               | 272                   | 273                 |
| Primary Efficacy (PE) population      | 249                   | 238                 |
| Safety population                     | 270                   | 267                 |
| Ongoing: On Study Treatment           | 1 <sup>[1]</sup>      | 0 <sup>[2]</sup>    |
| Ongoing: In Follow Up                 | 1 <sup>[3]</sup>      | 0 <sup>[4]</sup>    |
| Completed                             | 243                   | 233                 |
| Not completed                         | 29                    | 40                  |
| Physician decision                    | -                     | 2                   |

|  |    |    |
|--|----|----|
| Adverse event, non-fatal                           | 1  | 1  |
| Ongoing: On Study Treatment                        | 1  | -  |
| Other protocol defined stopping criteria           | 17 | 17 |
| Ongoing: In Follow Up                              | 1  | -  |
| Lost to follow-up                                  | 3  | 5  |
| Sponsor decision                                   | 1  | -  |
| Subject reached protocol defined stopping criteria | 1  | -  |
| Subject decided to withdraw from the study         | 4  | 15 |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to local regulations in China, data from Chinese subjects dated from 01-Jul-2016 onward was excluded. As noted in the primary CSR, the subject had been withdrawn from the study on 05 Apr 2011 due to being lost to follow-up, and overall survival was unknown. However, a data transition issue from the previous database (TRIO) led to the subject being incorrectly reported as "ongoing" for study arm "CapeOx plus Lapatinib"

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to local regulations in China (HGRAC), data collection at all sites in China was immediately stopped as of 01-Jul-2016. No data from Chinese subjects was transferred or processed thereafter. Consequently, one subject was marked as "ongoing" in the database for study arm "CapeOx plus Lapatinib"

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to local regulations in China (HGRAC), data collection at all sites in China was immediately stopped as of 01-Jul-2016. No data from Chinese subjects was transferred or processed thereafter. Consequently, one subject was marked as "ongoing" in the database for study arm "CapeOx plus Lapatinib"

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to local regulations in China, data from Chinese subjects dated from 01-Jul-2016 onward was excluded. As noted in the primary CSR, the subject had been withdrawn from the study on 05 Apr 2011 due to being lost to follow-up, and overall survival was unknown. However, a data transition issue from the previous database (TRIO) led to the subject being incorrectly reported as "ongoing" for study arm "CapeOx plus Lapatinib"

## Baseline characteristics

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | CapeOx plus Lapatinib |
|-----------------------|-----------------------|

Reporting group description:

Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m<sup>2</sup> intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m<sup>2</sup> per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m<sup>2</sup>/day after the first cycle at the investigator's discretion. 3) Lapatinib: 1250 mg orally once daily, starting on Day 1 and continued daily throughout the cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and lapatinib were continued until disease progression, unacceptable toxicity, or withdrawal of consent.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | CapeOx plus Placebo |
|-----------------------|---------------------|

Reporting group description:

Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m<sup>2</sup> intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m<sup>2</sup> per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m<sup>2</sup>/day after the first cycle at the investigator's discretion. 3) Lapatinib matching placebo: Taken orally once daily starting on Day 1 and continued throughout each cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and the lapatinib placebo were continued until disease progression, unacceptable toxicity, or withdrawal of consent.

| Reporting group values                             | CapeOx plus Lapatinib | CapeOx plus Placebo | Total |
|--|-----------------------|---------------------|-------|
| Number of subjects                                 | 272                   | 273                 | 545   |
| Age categorical                                    |                       |                     |       |
| Units: Subjects                                    |                       |                     |       |
| In utero   | 0                     | 0                   | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                     | 0                   | 0     |
| Newborns (0-27 days)                               | 0                     | 0                   | 0     |
| Infants and toddlers (28 days-23 months)           | 0                     | 0                   | 0     |
| Children (2-11 years)                              | 0                     | 0                   | 0     |
| Adolescents (12-17 years)                          | 0                     | 0                   | 0     |
| Adults (18-64 years)                               | 183                   | 185                 | 368   |
| From 65-84 years                                   | 88                    | 88                  | 176   |
| 85 years and over                                  | 1                     | 0                   | 1     |
| Gender categorical                                 |                       |                     |       |
| Units: Subjects                                    |                       |                     |       |
| Female   | 66                    | 73                  | 139   |
| Male   | 206                   | 200                 | 406   |
| GenderNIH  |                       |                     |       |
| Units: Subjects                                    |                       |                     |       |
| Female   | 66                    | 73                  | 139   |
| Male   | 206                   | 200                 | 406   |
| Race/Ethnicity, Customized                         |                       |                     |       |
| Units: Subjects                                    |                       |                     |       |
| African American/African Heritage (Hrtg)           | 2                     | 3                   | 5     |
| American Indian or Alaska Native                   | 3                     | 3                   | 6     |
| Central/South Asian Hrtg                           | 11                    | 3                   | 14    |

|   |     |     |     |
|---|-----|-----|-----|
| Japanese/East Asian Hrtg/South<br>East Asian Hrtg | 112 | 114 | 226 |
| White   | 144 | 150 | 294 |

  

|                    |         |         |   |
|--------------------|---------|---------|---|
| AgeContinuous      |         |         |   |
| Units: Years       |         |         |   |
| arithmetic mean    | 59.4    | 58.5    |   |
| standard deviation | ± 11.20 | ± 11.23 | - |



## End points

### End points reporting groups

|   |                       |
|---|-----------------------|
| Reporting group title   | CapeOx plus Lapatinib |
| Reporting group description:  |                       |
| Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m <sup>2</sup> intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m <sup>2</sup> per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m <sup>2</sup> /day after the first cycle at the investigator's discretion. 3) Lapatinib: 1250 mg orally once daily, starting on Day 1 and continued daily throughout the cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and lapatinib were continued until disease progression, unacceptable toxicity, or withdrawal of consent.                      |                       |
| Reporting group title   | CapeOx plus Placebo   |
| Reporting group description:  |                       |
| Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m <sup>2</sup> intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m <sup>2</sup> per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m <sup>2</sup> /day after the first cycle at the investigator's discretion. 3) Lapatinib matching placebo: Taken orally once daily starting on Day 1 and continued throughout each cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and the lapatinib placebo were continued until disease progression, unacceptable toxicity, or withdrawal of consent. |                       |

### Primary: Overall Survival in all randomized participants at the time of Primary Analysis

|   |   |
|---|---|
| End point title   | Overall Survival in all randomized participants at the time of Primary Analysis |
| End point description:  |   |
| Overall Survival was defined as the time from randomization to death from any cause. Participants who had not died were censored at their follow-up visit, either because follow-up had ended or was still ongoing. |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| From date of randomization till death due to any cause, assessed up the cut-off date for Primary Analysis (24-Sep-2012) (average of 4 years)  |   |

| End point values                 | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|----------------------------------|-----------------------|---------------------|--|--|
| Subject group type               | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed      | 272                   | 273                 |  |  |
| Units: Months                    |                       |                     |  |  |
| median (confidence interval 95%) | 11.9 (10.4 to 13.8)   | 10.4 (9.1 to 11.3)  |  |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | Primary Analysis: OS (ITT population)       |
| Comparison groups          | CapeOx plus Lapatinib v CapeOx plus Placebo |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 545                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.3244 <sup>[1]</sup> |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.91                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.74                    |
| upper limit                             | 1.1                     |

Notes:

[1] - Stratified log-rank test was conducted stratifying for prior adjuvant/neo-adjuvant treatment use and region.

### Primary: Overall Survival at the time of Primary Analysis

|                        |   |
|------------------------|---|
| End point title        | Overall Survival at the time of Primary Analysis  |
| End point description: | Overall Survival was defined as the time from randomization to death from any cause. Participants who had not died were censored at their follow-up visit, either because follow-up had ended or was still ongoing. |
| End point type         | Primary   |
| End point timeframe:   | From date of randomization till death due to any cause, assessed up the cut-off date for Primary Analysis (24-Sep-2012) (average of 4 years)  |

| End point values                 | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|----------------------------------|-----------------------|---------------------|--|--|
| Subject group type               | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed      | 249                   | 238                 |  |  |
| Units: Months                    |                       |                     |  |  |
| median (confidence interval 95%) | 12.2 (10.6 to 14.2)   | 10.5 (9.0 to 11.3)  |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Primary Analysis: OS (PE population)        |
| Comparison groups                       | CapeOx plus Lapatinib v CapeOx plus Placebo |
| Number of subjects included in analysis | 487   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           |   |
| P-value                                 | = 0.3492 <sup>[2]</sup>                     |
| Method                                  | Logrank                                     |
| Parameter estimate                      | Hazard ratio (HR)                           |
| Point estimate                          | 0.91  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.73    |
| upper limit         | 1.12    |

Notes:

[2] - Stratified log-rank test was conducted stratifying for prior adjuvant/neo-adjuvant treatment use and region.

### Secondary: Overall Survival at the time of Final Analysis

|                 |  |
|-----------------|--|
| End point title | Overall Survival at the time of Final Analysis |
|-----------------|--|

End point description:

Overall Survival was defined as the time from randomization to death from any cause. Participants who had not died were censored at their follow-up visit, either because follow-up had ended or was still ongoing.

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

End point timeframe:

From date of randomization till death due to any cause, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

| End point values                 | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|----------------------------------|-----------------------|---------------------|--|--|
| Subject group type               | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed      | 249                   | 238                 |  |  |
| Units: Months                    |                       |                     |  |  |
| median (confidence interval 95%) | 12.0 (10.4 to 13.8)   | 10.4 (9.0 to 11.3)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression Free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

Progression-Free Survival (PFS) was defined as the time from randomization to the earliest occurrence of disease progression or death from any cause. Per RECIST v1.0, progression was defined as at least a 20% increase in the sum of diameters of target lesions from the smallest recorded sum or the appearance of one or more new lesions. Participants with symptomatic progression, even without radiological confirmation, were also counted. Those who had neither progressed nor died were censored at their follow-up visit, either because follow-up had ended or was ongoing. Participants who received non-study anti-cancer therapies before progression were also censored.

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

End point timeframe:

From date of randomization till the earliest date of disease progression or death due to any cause, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

| End point values                 | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|----------------------------------|-----------------------|---------------------|--|--|
| Subject group type               | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed      | 249                   | 238                 |  |  |
| Units: Months                    |                       |                     |  |  |
| median (confidence interval 95%) | 6.2 (5.6 to 7.0)      | 5.4 (4.4 to 5.7)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with a confirmed Complete Response (CR) or a Partial Response (PR)

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with a confirmed Complete Response (CR) or a Partial Response (PR) |
|-----------------|---|

End point description:

A participant was considered a responder if they had achieved either a complete response (CR), defined as the disappearance of all target and non-target lesions, or a partial response (PR), defined as at least a 30% reduction in the sum of the longest diameters of target lesions from baseline, as assessed by the investigator and confirmed by radiographic imaging within four weeks of the initial observation.

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

End point timeframe:

From date of randomization till the date of the first documented response of CR or PR, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

| End point values            | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|-----------------------------|-----------------------|---------------------|--|--|
| Subject group type          | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed | 249                   | 238                 |  |  |
| Units: Participants         | 131                   | 94                  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with Clinical Benefit (CB)

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with Clinical Benefit (CB) |
|-----------------|---|

End point description:

Clinical Benefit (CB) was defined as evidence of a complete response (CR), partial response (PR), or stable disease (SD). CR referred to the disappearance of all target and non-target lesions, PR to at least a 30% reduction in the sum of the longest diameters of target lesions from baseline, and SD to neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progression, based on the smallest sum of diameters recorded since treatment initiation. All assessments were made by the investigator.

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

End point timeframe:

From date of randomization till date of disease progression (PD) or death due to any cause, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

| End point values            | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|-----------------------------|-----------------------|---------------------|--|--|
| Subject group type          | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed | 249                   | 238                 |  |  |
| Units: Participants         | 199                   | 188                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DOR)

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

End point description:

Duration of Response (DOR) was defined as the time from the first documented evidence of a complete response (CR) or partial response (PR) until the first recorded sign of disease progression or death from any cause. According to RECIST, progression was defined as at least a 20% increase in the sum of diameters of target lesions from the smallest recorded sum or the appearance of one or more new lesions. Participants who had neither progressed nor died were censored at their follow-up visit, either because follow-up had ended or was ongoing. Those who received non-study anti-cancer therapies before progression were also censored.

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

End point timeframe:

From the time of the first documented evidence of a confirmed CR or PR until the earliest date of disease progression or death due to any cause, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

| End point values                 | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|----------------------------------|-----------------------|---------------------|--|--|
| Subject group type               | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed      | 131                   | 94                  |  |  |
| Units: Months                    |                       |                     |  |  |
| median (confidence interval 95%) | 7.3 (6.4 to 8.5)      | 5.6 (4.6 to 6.0)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to response (TTR)

|                 |                        |
|-----------------|------------------------|
| End point title | Time to response (TTR) |
|-----------------|------------------------|

End point description:

Time to Response (TTR) was defined as the duration from randomization to the first documented evidence of either a complete response (CR) (the disappearance of all target and non-target lesions) or a partial response (PR) (at least a 30% reduction in the sum of the longest diameters of target lesions from baseline) as assessed by the investigator.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From date of randomization till the first documented evidence of confirmed CR or PR, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years) |           |

| End point values                 | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|----------------------------------|-----------------------|---------------------|--|--|
| Subject group type               | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed      | 131                   | 94                  |  |  |
| Units: Months                    |                       |                     |  |  |
| median (confidence interval 95%) | 1.4 (1.4 to 1.5)      | 1.4 (1.4 to 1.6)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with any on-therapy Adverse Event (AE) and Serious Adverse Event (SAE)

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with any on-therapy Adverse Event (AE) and Serious Adverse Event (SAE) |
|-----------------|---|

End point description:

An Adverse Event (AE) was defined as any untoward medical occurrence in a participant that was temporally associated with the use of a medicinal product, regardless of its causal relationship. This included any unfavorable or unintended sign (such as abnormal lab findings), symptom, or disease, whether new or worsened. A Serious Adverse Event (SAE) was defined as any such occurrence that, at any dose, resulted in death, was life-threatening, required hospitalization or its prolongation, caused disability or incapacity, led to a congenital anomaly or birth defect, or was a potential case of drug-induced liver injury.

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

End point timeframe:

From the first dose of study medication until 30 days after the last dose, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

| End point values                                | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|---|-----------------------|---------------------|--|--|
| Subject group type                              | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed                     | 270                   | 267                 |  |  |
| Units: Participants                             |                       |                     |  |  |
| On-Therapy AEs (All, regardless of seriousness) | 255                   | 237                 |  |  |
| On-Therapy SAEs                                 | 73                    | 54                  |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Percentage of participants with on-therapy Adverse Event (AE) by Maximum Grade**

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|                 |  |
|-----------------|--|
| End point title | Percentage of participants with on-therapy Adverse Event (AE) by Maximum Grade |
|-----------------|--|

End point description:

An Adverse Event (AE) was defined as any untoward medical occurrence in a participant that was temporally associated with the use of a medicinal product, regardless of its relationship to the product. This included any unfavorable or unintended sign (such as abnormal lab results), symptom, or disease, whether new or worsened. The severity of AEs was graded according to NCI CTCAE version 3.0: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death related to toxicity).

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

End point timeframe:

From the first dose of study medication until 30 days after the last dose, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

---

| End point values            | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|-----------------------------|-----------------------|---------------------|--|--|
| Subject group type          | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed | 255                   | 237                 |  |  |
| Units: Participants         |                       |                     |  |  |
| Grade 1                     | 43                    | 56                  |  |  |
| Grade 2                     | 85                    | 78                  |  |  |
| Grade 3                     | 94                    | 69                  |  |  |
| Grade 4                     | 17                    | 25                  |  |  |
| Grade 5                     | 16                    | 9                   |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Percentage of participants with on-therapy Serious Adverse Event (SAE) by Maximum Grade**

---

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with on-therapy Serious Adverse Event (SAE) by Maximum Grade |
|-----------------|---|

End point description:

A Serious Adverse Event (SAE) was defined as any such occurrence that resulted in death, was life-threatening, required hospitalization or its prolongation, caused disability or incapacity, led to a congenital anomaly or birth defect, or was a potential case of drug-induced liver injury. The severity of SAEs was graded according to NCI CTCAE version 3.0: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death related to toxicity).

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

End point timeframe:

From the first dose of study medication until 30 days after the last dose, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

---

| End point values            | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|-----------------------------|-----------------------|---------------------|--|--|
| Subject group type          | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed | 73                    | 54                  |  |  |
| Units: Participants         |                       |                     |  |  |
| Grade 1                     | 3                     | 3                   |  |  |
| Grade 2                     | 6                     | 4                   |  |  |
| Grade 3                     | 37                    | 21                  |  |  |
| Grade 4                     | 13                    | 18                  |  |  |
| Grade 5                     | 14                    | 8                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean change from Baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QOL) Questionnaire Core 30 (QLQ-C30) Domain Scores

|                 |   |
|-----------------|---|
| End point title | Mean change from Baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QOL) Questionnaire Core 30 (QLQ-C30) Domain Scores |
|-----------------|---|

End point description:

The EORTC QLQ-C30 is a comprehensive questionnaire developed for assessing the quality of life of cancer patients across different aspects including function scales namely physical, role, cognitive, emotional and social; symptom scales such as fatigue, pain, nausea and vomiting; and a global scale pronouncing overall health status. Its scoring method involves a 4-point Likert scale (ranging from 1 'Not at all' to 4 'Very Much'). Domain scores are calculated by averaging the items within the respective domain and then linearly transforming the score to fit within a 0-100 scale to finalize the scores. In terms of interpretation, a high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

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

End point timeframe:

From Baseline up to disease progression (PD), assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

| End point values                     | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|--------------------------------------|-----------------------|---------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed          | 61                    | 61                  |  |  |
| Units: Scores on a scale             |                       |                     |  |  |
| arithmetic mean (standard deviation) |                       |                     |  |  |
| Global health status/QoL             | -6.6 (± 24.63)        | -5.1 (± 23.97)      |  |  |
| Physical functioning                 | -9.4 (± 25.61)        | -9.6 (± 22.33)      |  |  |
| Role functioning                     | -8.9 (± 34.64)        | -11.7 (± 31.67)     |  |  |



|                        |                |                 |  |  |
|------------------------|----------------|-----------------|--|--|
| Emotional functioning  | -3.8 (± 27.37) | -7.1 (± 23.61)  |  |  |
| Cognitive functioning  | -7.4 (± 21.41) | -10.4 (± 21.98) |  |  |
| Social functioning     | -4.9 (± 32.54) | -0.5 (± 26.52)  |  |  |
| Fatigue                | 5.5 (± 26.42)  | 5.6 (± 25.30)   |  |  |
| Nausea and vomiting    | 3.3 (± 27.69)  | 4.4 (± 20.62)   |  |  |
| Pain                   | 4.9 (± 30.48)  | 7.7 (± 30.06)   |  |  |
| Dyspnoea               | 6.7 (± 26.61)  | 7.8 (± 27.70)   |  |  |
| Insomnia               | 0.0 (± 33.33)  | 3.3 (± 35.09)   |  |  |
| Appetite loss          | -0.5 (± 39.20) | 5.5 (± 37.11)   |  |  |
| Constipation           | -0.6 (± 32.18) | -3.8 (± 34.48)  |  |  |
| Diarrhoea              | 4.4 (± 29.49)  | 1.1 (± 23.95)   |  |  |
| Financial difficulties | 0.0 (± 29.81)  | 0.6 (± 24.16)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean change from Baseline in the EORTC Quality of Life (QOL) Questionnaire of Stomach 22 (QLQ-STO22) Scales/Items Score Scale

|                 |   |
|-----------------|---|
| End point title | Mean change from Baseline in the EORTC Quality of Life (QOL) Questionnaire of Stomach 22 (QLQ-STO22) Scales/Items Score Scale |
|-----------------|---|

End point description:

The QLQ-STO22 consists of 22 items divided into five subscales: dysphagia, pain, reflux, eating restrictions and anxiety, as well as single items addressing dry mouth, body image, taste, and hair loss. Each item is answered on a 4-point scale, ranging from 1 (not at all) to 4 (very much). Raw scores for each subscale or single item are calculated by averaging the scores of the individual items that make up the scale. These scores are then linearly transformed to range from 0 to 100. In terms of interpretation, a higher score indicates a worse quality of life concerning the specific symptoms assessed.

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

End point timeframe:

From Baseline up to disease progression (PD), assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

| End point values                     | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|--------------------------------------|-----------------------|---------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed          | 60                    | 54                  |  |  |
| Units: Scores on a scale             |                       |                     |  |  |
| arithmetic mean (standard deviation) |                       |                     |  |  |
| Dysphagia scale                      | 3.4 (± 22.99)         | -3.1 (± 16.92)      |  |  |
| Pain scale                           | -1.5 (± 22.20)        | -0.6 (± 18.71)      |  |  |
| Reflux scale                         | -1.4 (± 21.86)        | -4.1 (± 18.48)      |  |  |
| Eating restrictions scale            | 1.2 (± 27.83)         | -3.2 (± 22.11)      |  |  |
| Anxiety scale                        | -2.9 (± 27.42)        | -7.5 (± 24.38)      |  |  |
| Dry mouth scale                      | 2.8 (± 31.13)         | 1.9 (± 32.00)       |  |  |
| Taste scale                          | 4.5 (± 37.37)         | 9.2 (± 32.03)       |  |  |
| Body image scale                     | -3.3 (± 37.68)        | -1.9 (± 30.66)      |  |  |

|                 |                 |               |  |  |
|-----------------|-----------------|---------------|--|--|
| Hair loss scale | -16.7 (± 23.57) | 0.0 (± 33.33) |  |  |
|-----------------|-----------------|---------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean change from Baseline in Utility Score (Health Utility Index) in the EuroQoL-5 Dimensions (EQ-5D) Questionnaire

|                 |   |
|-----------------|---|
| End point title | Mean change from Baseline in Utility Score (Health Utility Index) in the EuroQoL-5 Dimensions (EQ-5D) Questionnaire |
|-----------------|---|

End point description:

The EQ-5D is a standardized instrument developed by the EuroQoL Group to measure health-related quality of life. It includes a descriptive system covering five dimensions and a Visual Analogue Scale (VAS), often referred to as the Thermometer Score.

The Utility Score (Health Utility Index) is derived from the five dimensions of the EQ-5D descriptive system (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has levels indicating severity (e.g., 1 = no problems, 2 = some problems, 3 = extreme problems). These combinations form a health state, which is then converted into a single index value using a country-specific value set. In the UK-based value set, the possible EQ-5D index utility values range from -0.594 to 1.0, where: 1.0 = perfect health, 0 = death and < 0 = health states considered worse than death.

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

End point timeframe:

From Baseline up to disease progression (PD), assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

| End point values                     | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|--------------------------------------|-----------------------|---------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed          | 59                    | 57                  |  |  |
| Units: Scores on a scale             |                       |                     |  |  |
| arithmetic mean (standard deviation) | -0.17 (± 0.347)       | -0.07 (± 0.328)     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean change from Baseline in Thermometer Score (EQ VAS) in the EuroQoL-5 Dimensions (EQ-5D) Questionnaire

|                 |   |
|-----------------|---|
| End point title | Mean change from Baseline in Thermometer Score (EQ VAS) in the EuroQoL-5 Dimensions (EQ-5D) Questionnaire |
|-----------------|---|

End point description:

The EQ-5D is a standardized instrument developed by the EuroQoL Group to measure health-related quality of life. It includes a descriptive system covering five dimensions and a Visual Analogue Scale (VAS), often referred to as the Thermometer Score.

The Thermometer Score is a self-rated health score using a vertical visual analogue scale , where

respondents rate their overall health on a scale from 0 (worst imaginable health) to 100 (best imaginable health).

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| From Baseline up to disease progression (PD), assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years) |           |

| End point values                     | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|--------------------------------------|-----------------------|---------------------|--|--|
| Subject group type                   | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed          | 61                    | 60                  |  |  |
| Units: Scores on a scale             |                       |                     |  |  |
| arithmetic mean (standard deviation) | -4.61 (± 23.054)      | -7.90 (± 17.349)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with worst-case on-therapy Chemistry Toxicities

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with worst-case on-therapy Chemistry Toxicities |
|-----------------|--|

End point description:

The severity of chemistry parameters was graded according to NCI CTCAE version 3.0: Grade 0 (No adverse event or within normal limits), Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) and Grade 4 (life-threatening).

Chemistry data included: Alanine aminotransferase (ALT), Albumin, Alkaline phosphatases (ALP), Aspartate aminotransferase (AST), Calcium (hypercalcemia), Calcium (hypocalcemia), Creatine Kinase (CK), Creatine, Glucose (hyperglycemia), Glucose (hypoglycemia), Magnesium (hypermagnesemia), Magnesium (hypomagnesemia), Potassium (hyperkalemia), Potassium (hypokalemia), Sodium (hypernatremia), Sodium (hyponatremia) and Total Bilirubin.

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

End point timeframe:

From the first dose of study medication until 30 days after the last dose, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

| End point values                         | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|--|-----------------------|---------------------|--|--|
| Subject group type                       | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed              | 260                   | 262                 |  |  |
| Units: Participants                      |                       |                     |  |  |
| Alanine aminotransferase (ALT) Grade 0   | 163                   | 153                 |  |  |
| Albumin Grade 0                          | 123                   | 140                 |  |  |
| Alkaline phosphatases (ALP) Grade 0      | 120                   | 114                 |  |  |
| Aspartate aminotransferase (AST) Grade 0 | 108                   | 93                  |  |  |

|  |     |     |  |  |
|--|-----|-----|--|--|
| Calcium (hypercalcemia) Grade 0          | 237 | 242 |  |  |
| Calcium (hypocalcemia) Grade 0           | 129 | 134 |  |  |
| Creatine Kinase (CK) Grade 0             | 1   | 3   |  |  |
| Creatinine Grade 0                       | 230 | 228 |  |  |
| Glucose (hyperglycemia) Grade 0          | 107 | 119 |  |  |
| Glucose (hypoglycemia) Grade 0           | 223 | 237 |  |  |
| Magnesium (hypermagnesemia) Grade 0      | 229 | 234 |  |  |
| Magnesium (hypomagnesemia) Grade 0       | 189 | 199 |  |  |
| Potassium (hyperkalemia) Grade 0         | 228 | 234 |  |  |
| Potassium (hypokalemia) Grade 0          | 160 | 195 |  |  |
| Sodium (hypernatremia) Grade 0           | 234 | 234 |  |  |
| Sodium (hyponatremia) Grade 0            | 186 | 199 |  |  |
| Total Bilirubin Grade 0                  | 153 | 178 |  |  |
| Alanine aminotransferase (ALT) Grade 1   | 87  | 94  |  |  |
| Albumin Grade 1                          | 72  | 66  |  |  |
| Alkaline phosphatases (ALP) Grade 1      | 113 | 109 |  |  |
| Aspartate aminotransferase (AST) Grade 1 | 133 | 142 |  |  |
| Calcium (hypercalcemia) Grade 1          | 17  | 19  |  |  |
| Calcium (hypocalcemia) Grade 1           | 74  | 81  |  |  |
| Creatine Kinase (CK) Grade 1             | 0   | 0   |  |  |
| Creatinine Grade 1                       | 21  | 33  |  |  |
| Glucose (hyperglycemia) Grade 1          | 115 | 103 |  |  |
| Glucose (hypoglycemia) Grade 1           | 32  | 20  |  |  |
| Magnesium (hypermagnesemia) Grade 1      | 20  | 17  |  |  |
| Magnesium (hypomagnesemia) Grade 1       | 59  | 52  |  |  |
| Potassium (hyperkalemia) Grade 1         | 20  | 14  |  |  |
| Potassium (hypokalemia) Grade 1          | 75  | 54  |  |  |
| Sodium (hypernatremia) Grade 1           | 18  | 20  |  |  |
| Sodium (hyponatremia) Grade 1            | 52  | 42  |  |  |
| Total Bilirubin Grade 1                  | 55  | 42  |  |  |
| Alanine aminotransferase (ALT) Grade 2   | 8   | 11  |  |  |
| Albumin Grade 2                          | 59  | 48  |  |  |
| Alkaline phosphatases (ALP) Grade 2      | 22  | 25  |  |  |
| Aspartate aminotransferase (AST) Grade 2 | 16  | 21  |  |  |
| Calcium (hypercalcemia) Grade 2          | 2   | 1   |  |  |
| Calcium (hypocalcemia) Grade 2           | 50  | 43  |  |  |
| Creatine Kinase (CK) Grade 2             | 0   | 0   |  |  |
| Creatinine Grade 2                       | 7   | 0   |  |  |
| Glucose (hyperglycemia) Grade 2          | 30  | 32  |  |  |
| Glucose (hypoglycemia) Grade 2           | 3   | 2   |  |  |
| Magnesium (hypermagnesemia) Grade 2      | 0   | 0   |  |  |
| Magnesium (hypomagnesemia) Grade 2       | 5   | 5   |  |  |
| Potassium (hyperkalemia) Grade 2         | 8   | 11  |  |  |
| Potassium (hypokalemia) Grade 2          | 0   | 0   |  |  |
| Sodium (hypernatremia) Grade 2           | 2   | 5   |  |  |
| Sodium (hyponatremia) Grade 2            | 0   | 0   |  |  |
| Total Bilirubin Grade 2                  | 43  | 33  |  |  |
| Alanine aminotransferase (ALT) Grade 3   | 2   | 4   |  |  |

|  |    |    |  |  |
|--|----|----|--|--|
| Albumin Grade 3                          | 3  | 4  |  |  |
| Alkaline phosphatases (ALP) Grade 3      | 5  | 12 |  |  |
| Aspartate aminotransferase (AST) Grade 3 | 3  | 6  |  |  |
| Calcium (hypercalcemia) Grade 3          | 0  | 0  |  |  |
| Calcium (hypocalcemia) Grade 3           | 3  | 4  |  |  |
| Creatine Kinase (CK) Grade 3             | 0  | 0  |  |  |
| Creatinine Grade 3                       | 2  | 1  |  |  |
| Glucose (hyperglycemia) Grade 3          | 6  | 8  |  |  |
| Glucose (hypoglycemia) Grade 3           | 1  | 1  |  |  |
| Magnesium (hypermagnesemia) Grade 3      | 5  | 5  |  |  |
| Magnesium (hypomagnesemia) Grade 3       | 1  | 0  |  |  |
| Potassium (hyperkalemia) Grade 3         | 2  | 2  |  |  |
| Potassium (hypokalemia) Grade 3          | 21 | 11 |  |  |
| Sodium (hypernatremia) Grade 3           | 3  | 2  |  |  |
| Sodium (hyponatremia) Grade 3            | 19 | 16 |  |  |
| Total Bilirubin Grade 3                  | 7  | 3  |  |  |
| Alanine aminotransferase (ALT) Grade 4   | 0  | 0  |  |  |
| Albumin Grade 4                          | 0  | 0  |  |  |
| Alkaline phosphatases (ALP) Grade 4      | 0  | 0  |  |  |
| Aspartate aminotransferase (AST) Grade 4 | 0  | 0  |  |  |
| Calcium (hypercalcemia) Grade 4          | 0  | 0  |  |  |
| Calcium (hypocalcemia) Grade 4           | 0  | 0  |  |  |
| Creatine Kinase (CK) Grade 4             | 0  | 0  |  |  |
| Creatinine Grade 4                       | 0  | 0  |  |  |
| Glucose (hyperglycemia) Grade 4          | 1  | 0  |  |  |
| Glucose (hypoglycemia) Grade 4           | 0  | 2  |  |  |
| Magnesium (hypermagnesemia) Grade 4      | 0  | 0  |  |  |
| Magnesium (hypomagnesemia) Grade 4       | 0  | 0  |  |  |
| Potassium (hyperkalemia) Grade 4         | 1  | 0  |  |  |
| Potassium (hypokalemia) Grade 4          | 3  | 1  |  |  |
| Sodium (hypernatremia) Grade 4           | 2  | 0  |  |  |
| Sodium (hyponatremia) Grade 4            | 2  | 4  |  |  |
| Total Bilirubin Grade 4                  | 2  | 5  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with worst-case on-therapy Hematologic Toxicities

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with worst-case on-therapy Hematologic Toxicities |
|-----------------|--|

End point description:

The severity of hematologic parameters was graded according to NCI CTCAE version 3.0: Grade 0 (No adverse event or within normal limits), Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) and Grade 4 (life-threatening).

Hematology data included: Hemoglobin, Platelet count, Total Neutrophils (Total ANC - Total Absolute Neutrophil Count) and White Blood Cell count.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| From the first dose of study medication until 30 days after the last dose, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years) |           |

| End point values                              | CapeOx plus Lapatinib | CapeOx plus Placebo |  |  |
|---|-----------------------|---------------------|--|--|
| Subject group type                            | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed                   | 261                   | 263                 |  |  |
| Units: Participants                           |                       |                     |  |  |
| Hemoglobin Grade 0                            | 18                    | 22                  |  |  |
| Platelet count Grade 0                        | 97                    | 116                 |  |  |
| Total ANC (Absolute Neutrophil Count) Grade 0 | 112                   | 127                 |  |  |
| White Blood Cell count Grade 0                | 126                   | 136                 |  |  |
| Hemoglobin Grade 1                            | 104                   | 121                 |  |  |
| Platelet count Grade 1                        | 95                    | 86                  |  |  |
| Total ANC (Absolute Neutrophil Count) Grade 1 | 42                    | 45                  |  |  |
| White Blood Cell count Grade 1                | 71                    | 74                  |  |  |
| Hemoglobin Grade 2                            | 104                   | 93                  |  |  |
| Platelet count Grade 2                        | 43                    | 27                  |  |  |
| Total ANC (Absolute Neutrophil Count) Grade 2 | 58                    | 48                  |  |  |
| White Blood Cell count Grade 2                | 50                    | 47                  |  |  |
| Hemoglobin Grade 3                            | 35                    | 27                  |  |  |
| Platelet count Grade 3                        | 21                    | 30                  |  |  |
| Total ANC (Absolute Neutrophil Count) Grade 3 | 22                    | 27                  |  |  |
| White Blood Cell count Grade 3                | 12                    | 4                   |  |  |
| Hemoglobin Grade 4                            | 0                     | 0                   |  |  |
| Platelet count Grade 4                        | 5                     | 2                   |  |  |
| Total ANC (Absolute Neutrophil Count) Grade 4 | 6                     | 2                   |  |  |
| White Blood Cell count Grade 4                | 2                     | 1                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were documented from the first administration of the study medication through the end of the Long-Term Follow-up (LTFU) period, covering a duration of up to approximately 16 years.

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 | 27.1 |
|--------------------|------|

### Reporting groups

|                       |                            |
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| Reporting group title | CapeOx + Lapatinib 1250 mg |
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Reporting group description:

CapeOx + Lapatinib 1250 mg

|                       |                  |
|-----------------------|------------------|
| Reporting group title | CapeOx + Placebo |
|-----------------------|------------------|

Reporting group description:

CapeOx + Placebo

| Serious adverse events  | CapeOx + Lapatinib<br>1250 mg | CapeOx + Placebo  |  |
|---|-------------------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                               |                   |  |
| subjects affected / exposed   | 73 / 270 (27.04%)             | 54 / 267 (20.22%) |  |
| number of deaths (all causes)                                       | 42                            | 40                |  |
| number of deaths resulting from adverse events                      | 4                             | 1                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                               |                   |  |
| Tumour haemorrhage  |                               |                   |  |
| subjects affected / exposed   | 1 / 270 (0.37%)               | 0 / 267 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1                         | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0                         | 0 / 0             |  |
| Vascular disorders  |                               |                   |  |
| Haemorrhage   |                               |                   |  |
| subjects affected / exposed   | 1 / 270 (0.37%)               | 0 / 267 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1                         | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0                         | 0 / 0             |  |
| Deep vein thrombosis  |                               |                   |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Circulatory collapse                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Venous thrombosis                                    |                 |                 |  |
| subjects affected / exposed                          | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia   |                 |                 |  |
| subjects affected / exposed                          | 2 / 270 (0.74%) | 4 / 267 (1.50%) |  |
| occurrences causally related to treatment / all      | 2 / 2           | 3 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Condition aggravated                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Death  |                 |                 |  |
| subjects affected / exposed                          | 2 / 270 (0.74%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 2           | 0 / 0           |  |
| Drowning   |                 |                 |  |
| subjects affected / exposed                          | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |
| Fatigue  |                 |                 |  |
| subjects affected / exposed                          | 3 / 270 (1.11%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all      | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Multiple organ dysfunction syndrome                  |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Oedema peripheral                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sudden death                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pyrexia   |                 |                 |  |
| subjects affected / exposed                     | 4 / 270 (1.48%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Drug hypersensitivity                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Contrast media reaction                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Pharyngeal haemorrhage                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchospasm                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Pulmonary infarction                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 270 (1.11%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Product issues                                  |                 |                 |  |
| Device occlusion                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemoglobin decreased                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood bilirubin increased                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver function test abnormal                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Weight decreased                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ejection fraction decreased                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Face injury                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal cord injury thoracic                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Pericardial effusion                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular dysfunction                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiac tamponade                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Aphasia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epilepsy  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Haemorrhage intracranial                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorder                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraesthesia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure   |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Speech disorder                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |  |
| <b>Anaemia</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 7 / 270 (2.59%) | 4 / 267 (1.50%) |  |
| occurrences causally related to treatment / all | 4 / 9           | 4 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| <b>Thrombocytopenia</b>                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Neutropenia</b>                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 270 (1.11%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal disorders</b>               |                 |                 |  |
| <b>Abdominal pain</b>                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 3 / 267 (1.12%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| <b>Haematemesis</b>                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| <b>Gingival bleeding</b>                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal obstruction</b>             |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal haemorrhage</b>             |                 |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 3 / 270 (1.11%)  | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastric haemorrhage                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%)  | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastric dilatation                              |                  |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%)  | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Enterocutaneous fistula                         |                  |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%)  | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Dysphagia                                       |                  |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%)  | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diarrhoea                                       |                  |                 |  |
| subjects affected / exposed                     | 16 / 270 (5.93%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 20 / 20          | 1 / 1           |  |
| deaths causally related to treatment / all      | 2 / 2            | 0 / 0           |  |
| Ascites   |                  |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%)  | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Abdominal pain upper                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%)  | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Ileus spastic                                   |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 6 / 270 (2.22%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 5 / 6           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mesenteric vein thrombosis                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Melaena   |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine perforation                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Obstruction gastric                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 2 / 267 (0.75%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 7 / 270 (2.59%) | 6 / 267 (2.25%) |  |
| occurrences causally related to treatment / all | 4 / 7           | 6 / 6           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Jaundice cholestatic                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaundice  |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oliguria  |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abdominal infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal infection                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine infection                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Lung abscess                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 6 / 270 (2.22%) | 3 / 267 (1.12%) |  |
| occurrences causally related to treatment / all | 1 / 6           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumonia aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 1           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 0 / 270 (0.00%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 4 / 270 (1.48%) | 3 / 267 (1.12%) |  |
| occurrences causally related to treatment / all | 3 / 4           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 6 / 270 (2.22%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 4 / 6           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 270 (0.37%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 1 / 267 (0.37%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 270 (0.74%) | 0 / 267 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | CapeOx + Lapatinib<br>1250 mg | CapeOx + Placebo   |  |
|---|-------------------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                               |                    |  |
| subjects affected / exposed                           | 243 / 270 (90.00%)            | 214 / 267 (80.15%) |  |
| Investigations  |                               |                    |  |
| Weight decreased                                      |                               |                    |  |
| subjects affected / exposed                           | 43 / 270 (15.93%)             | 33 / 267 (12.36%)  |  |
| occurrences (all)                                     | 44                            | 33                 |  |
| Nervous system disorders                              |                               |                    |  |
| Dizziness   |                               |                    |  |
| subjects affected / exposed                           | 14 / 270 (5.19%)              | 14 / 267 (5.24%)   |  |
| occurrences (all)                                     | 17                            | 19                 |  |
| Peripheral sensory neuropathy                         |                               |                    |  |
| subjects affected / exposed                           | 34 / 270 (12.59%)             | 29 / 267 (10.86%)  |  |
| occurrences (all)                                     | 69                            | 64                 |  |
| Neuropathy peripheral                                 |                               |                    |  |
| subjects affected / exposed                           | 53 / 270 (19.63%)             | 58 / 267 (21.72%)  |  |
| occurrences (all)                                     | 70                            | 81                 |  |

|   |                           |                          |  |
|---|---------------------------|--------------------------|--|
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 7 / 270 (2.59%)<br>8      | 14 / 267 (5.24%)<br>18   |  |
| General disorders and administration site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences (all) | 30 / 270 (11.11%)<br>46   | 26 / 267 (9.74%)<br>38   |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)   | 14 / 270 (5.19%)<br>16    | 18 / 267 (6.74%)<br>20   |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 64 / 270 (23.70%)<br>89   | 60 / 267 (22.47%)<br>100 |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)  | 46 / 270 (17.04%)<br>55   | 36 / 267 (13.48%)<br>43  |  |
| Gastrointestinal disorders<br>Abdominal distension<br>subjects affected / exposed<br>occurrences (all)              | 16 / 270 (5.93%)<br>23    | 9 / 267 (3.37%)<br>9     |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)  | 27 / 270 (10.00%)<br>34   | 32 / 267 (11.99%)<br>45  |  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)  | 20 / 270 (7.41%)<br>22    | 27 / 267 (10.11%)<br>31  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)  | 30 / 270 (11.11%)<br>33   | 54 / 267 (20.22%)<br>72  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 146 / 270 (54.07%)<br>325 | 77 / 267 (28.84%)<br>157 |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)   | 14 / 270 (5.19%)<br>17    | 20 / 267 (7.49%)<br>24   |  |
| Nausea  |                           |                          |  |

|   |                    |                    |  |
|---|--------------------|--------------------|--|
| subjects affected / exposed                     | 128 / 270 (47.41%) | 113 / 267 (42.32%) |  |
| occurrences (all)                               | 270                | 266                |  |
| Stomatitis                                      |                    |                    |  |
| subjects affected / exposed                     | 19 / 270 (7.04%)   | 10 / 267 (3.75%)   |  |
| occurrences (all)                               | 21                 | 12                 |  |
| Vomiting  |                    |                    |  |
| subjects affected / exposed                     | 116 / 270 (42.96%) | 93 / 267 (34.83%)  |  |
| occurrences (all)                               | 207                | 204                |  |
| Respiratory, thoracic and mediastinal disorders |                    |                    |  |
| Cough   |                    |                    |  |
| subjects affected / exposed                     | 12 / 270 (4.44%)   | 19 / 267 (7.12%)   |  |
| occurrences (all)                               | 15                 | 22                 |  |
| Skin and subcutaneous tissue disorders          |                    |                    |  |
| Pruritus  |                    |                    |  |
| subjects affected / exposed                     | 18 / 270 (6.67%)   | 5 / 267 (1.87%)    |  |
| occurrences (all)                               | 22                 | 7                  |  |
| Palmar-plantar erythrodysaesthesia syndrome     |                    |                    |  |
| subjects affected / exposed                     | 57 / 270 (21.11%)  | 40 / 267 (14.98%)  |  |
| occurrences (all)                               | 71                 | 47                 |  |
| Rash  |                    |                    |  |
| subjects affected / exposed                     | 46 / 270 (17.04%)  | 16 / 267 (5.99%)   |  |
| occurrences (all)                               | 51                 | 17                 |  |
| Skin hyperpigmentation                          |                    |                    |  |
| subjects affected / exposed                     | 16 / 270 (5.93%)   | 7 / 267 (2.62%)    |  |
| occurrences (all)                               | 16                 | 7                  |  |
| Musculoskeletal and connective tissue disorders |                    |                    |  |
| Back pain                                       |                    |                    |  |
| subjects affected / exposed                     | 9 / 270 (3.33%)    | 16 / 267 (5.99%)   |  |
| occurrences (all)                               | 10                 | 17                 |  |
| Metabolism and nutrition disorders              |                    |                    |  |
| Decreased appetite                              |                    |                    |  |
| subjects affected / exposed                     | 107 / 270 (39.63%) | 85 / 267 (31.84%)  |  |
| occurrences (all)                               | 163                | 151                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 05 May 2008       | Amendment 1: Update of the safety monitoring for hepatotoxicity; clarification of screening assessments; administrative changes.  |
| 13 August 2008    | Amendment 2: Administrative update and pharmacokinetic sample was appended to the supplemental liver chemistry follow-up criteria sample panel to obtain serum levels of the study treatment (lapatinib).   |
| 10 September 2009 | Amendment 3: Revision to statistical plan; administrative updates; clarification of operational elements and text   |
| 28 October 2010   | Amendment 4: Clarification to prior use of oxaliplatin; updated prohibited medications table; elimination of collection of serum and RNA blood samples; administrative updates and clarifications to enhance consistency and quality of document, removal from the protocol of supportive care guidance (Appendix 5), to be placed in Study Procedures Manual   |
| 22 August 2011    | Amendment 5: Statistical revisions: the definition of the primary efficacy population was revised to include all subjects centrally confirmed by FISH, whether or not the subject had taken study medication. The addition of per protocol population to support the sensitivity analysis of selective efficacy data in subjects who comply most closely with the intended protocol population and updated clarifications in prohibited medications table. Administration changes and clarification of operational procedures to enhance protocol uniformity  |
| 28 September 2011 | Amendment 5: republished due to discrepancy in headers. No changes to the body of the protocol  |
| 13 December 2011  | Amendment 6: Local amendment for sites in China to allow continuation of recruitment given the Chinese regulatory authority's requirement for a minimum number of local subjects to participate in the study. Of note, no additional subjects were enrolled   |
| 06 March 2014     | Amendment 7: This amendment is being implemented to discontinue collection of many studies specific assessments while allowing subjects currently on study treatment to have continued access to this treatment until the occurrence of unacceptable toxicity or disease progression (as determined by the Investigator) or withdrawal for any reasons. The aim is to continue to protect the safety of the subject, whilst removing the requirement for assessments intended to collect further efficacy data, unless clinically indicate; Amendment of study assessments: clinical assessments of safety and efficacy will be performed as directed by the Investigator judgment; Amendment to stop data collection for all subjects currently on follow -up; To ensure the safety of the subjects, Investigators will be asked to collect and report to the Sponsor all serious adverse events (SAEs) and pregnancies, and date and reasons for study treatment discontinuation (including adverse events (AEs) leading to discontinuation of study treatment and all other reasons for discontinuation of study treatment |
| 27 April 2015     | Amendment 8: Clarification to lapatinib drug supply, liver event data collection and interval of long-term follow-up period   |
| 22 March 2016     | Amendment 9: Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. Make administrative changes to align with Novartis processes and procedures   |

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported