



Clinical trial results:

A Randomized, Multicenter, Phase III Open-label Study of the Efficacy and Safety of Trastuzumab MCC-DM1 vs. Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer Who Have Received Prior Trastuzumab-Based Therapy

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2008-005713-22 |
| Trial protocol | ES DE SE PT DK FR SI GB BG FI IT |
| Global end of trial date | 23 September 2015 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 29 September 2016 |
| First version publication date | 29 September 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BO21977 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-----------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00829166 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Protocol ID: TDM4370g |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 December 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 September 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- To compare the efficacy of trastuzumab emtansine versus capecitabine plus lapatinib in participants with human epidermal growth factor receptor 2 (HER2)-positive, unresectable, locally advanced breast cancer or metastatic breast cancer (MBC) as measured by progression-free survival (PFS) based on an independent review of tumor assessments, overall survival (OS), and to assess landmark (1-year and 2-year) survival rates within each treatment group, as appropriate
- To assess the safety of trastuzumab emtansine relative to the safety of capecitabine plus lapatinib

Protection of trial subjects:

This study was conducted in accordance with Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (October 1996), and applicable local, state, and federal laws, as well as other applicable country laws.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 23 February 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | United States: 270 |
| Country: Number of subjects enrolled | Korea, Republic of: 103 |
| Country: Number of subjects enrolled | Canada: 73 |
| Country: Number of subjects enrolled | France: 64 |
| Country: Number of subjects enrolled | United Kingdom: 56 |
| Country: Number of subjects enrolled | Brazil: 55 |
| Country: Number of subjects enrolled | Italy: 52 |
| Country: Number of subjects enrolled | Poland: 49 |
| Country: Number of subjects enrolled | Germany: 47 |
| Country: Number of subjects enrolled | Spain: 39 |
| Country: Number of subjects enrolled | Bulgaria: 38 |
| Country: Number of subjects enrolled | Taiwan: 28 |
| Country: Number of subjects enrolled | Singapore: 22 |
| Country: Number of subjects enrolled | Switzerland: 14 |
| Country: Number of subjects enrolled | Sweden: 14 |
| Country: Number of subjects enrolled | Russian Federation: 12 |
| Country: Number of subjects enrolled | Mexico: 11 |

| | |
|--------------------------------------|---------------------------|
| Country: Number of subjects enrolled | Portugal: 11 |
| Country: Number of subjects enrolled | Finland: 10 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 8 |
| Country: Number of subjects enrolled | Slovenia: 7 |
| Country: Number of subjects enrolled | Hong Kong: 3 |
| Country: Number of subjects enrolled | Philippines: 2 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | India: 1 |
| Country: Number of subjects enrolled | New Zealand: 1 |
| Worldwide total number of subjects | 991 |
| EEA total number of subjects | 388 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 853 |
| From 65 to 84 years | 138 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants of "Lapatinib + Capecitabine" arm were allowed to cross over to receive trastuzumab emtansine based on statistically significant Overall Survival (OS) benefit in favor of trastuzumab emtansine demonstrated in second interim analysis (cut-off date 31 July 2012). The safety analysis of the arm was then reported.

Period 1

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

Arms

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

| | |
|------------------|-----------------------|
| Arm title | Trastuzumab Emtansine |
|------------------|-----------------------|

Arm description:

Participants received trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) intravenous (IV) infusion over 30-90 minutes on Day 1 of each 21-day treatment cycle until disease progression (PD) (as assessed by the investigator), unmanageable toxicity, or study termination.

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

Dosage and administration details:

Trastuzumab emtansine 3.6 mg/kg IV infusion over 30-90 minutes on Day 1 of each 21-day treatment cycle.

| | |
|------------------|--------------------------|
| Arm title | Lapatinib + Capecitabine |
|------------------|--------------------------|

Arm description:

Participants received lapatinib 1250 mg (five 250 mg tablets) orally once daily during each 21-day cycle + capecitabine 1000 milligrams per square meter (mg/m²) orally twice daily on Days 1-14 of each 21-day treatment cycle until PD (as assessed by the investigator), unmanageable toxicity, or study termination. Participants of this group were allowed to cross over to receive trastuzumab emtansine based on statistically significant OS benefit in favor of trastuzumab emtansine demonstrated in second interim analysis.

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

Dosage and administration details:

Lapatinib 1250 mg (five 250 mg tablets) orally once daily during each 21-day cycle.

| | |
|--|--------------------|
| 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:

Capecitabine 1000 mg/m² orally twice daily on Days 1-14 of each 21-day treatment cycle.

| Number of subjects in period 1 | Trastuzumab Emtansine | Lapatinib + Capecitabine |
|---------------------------------------|--------------------------|-----------------------------|
| Started | 495 | 496 |
| Treated | 490 | 488 |
| Completed | 0 | 0 |
| Not completed | 495 | 496 |
| Physician decision | 4 | 3 |
| Death | 305 | 333 |
| Subject's Decision | 41 | 55 |
| Sponsor's Decision | 137 | 98 |
| Not Specified | 3 | 3 |
| Lost to follow-up | 5 | 4 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Trastuzumab Emtansine |
|-----------------------|-----------------------|

Reporting group description:

Participants received trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) intravenous (IV) infusion over 30-90 minutes on Day 1 of each 21-day treatment cycle until disease progression (PD) (as assessed by the investigator), unmanageable toxicity, or study termination.

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

Reporting group description:

Participants received lapatinib 1250 mg (five 250 mg tablets) orally once daily during each 21-day cycle + capecitabine 1000 milligrams per square meter (mg/m²) orally twice daily on Days 1-14 of each 21-day treatment cycle until PD (as assessed by the investigator), unmanageable toxicity, or study termination. Participants of this group were allowed to cross over to receive trastuzumab emtansine based on statistically significant OS benefit in favor of trastuzumab emtansine demonstrated in second interim analysis.

| Reporting group values | Trastuzumab Emtansine | Lapatinib + Capecitabine | Total |
|---|-----------------------|--------------------------|-------|
| Number of subjects | 495 | 496 | 991 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 52.2 ± 11 | 53.2 ± 10.8 | - |
| Gender categorical Units: Subjects | | | |
| Female | 494 | 492 | 986 |
| Male | 1 | 4 | 5 |

End points

End points reporting groups

| | |
|---|--------------------------|
| Reporting group title | Trastuzumab Emtansine |
| Reporting group description: Participants received trastuzumab emtansine 3.6 milligrams per kilogram (mg/kg) intravenous (IV) infusion over 30-90 minutes on Day 1 of each 21-day treatment cycle until disease progression (PD) (as assessed by the investigator), unmanageable toxicity, or study termination. | |
| Reporting group title | Lapatinib + Capecitabine |
| Reporting group description: Participants received lapatinib 1250 mg (five 250 mg tablets) orally once daily during each 21-day cycle + capecitabine 1000 milligrams per square meter (mg/m ²) orally twice daily on Days 1-14 of each 21-day treatment cycle until PD (as assessed by the investigator), unmanageable toxicity, or study termination. Participants of this group were allowed to cross over to receive trastuzumab emtansine based on statistically significant OS benefit in favor of trastuzumab emtansine demonstrated in second interim analysis. | |

Primary: Percentage of Participants With PD or Death as Assessed by an Independent Review Committee (IRC)

| | |
|--|---|
| End point title | Percentage of Participants With PD or Death as Assessed by an Independent Review Committee (IRC) ^[1] |
| End point description: PD was assessed by an IRC using modified Response Evaluation Criteria in Solid Tumors (RECIST). All measurable lesions up to a maximum of 5 per organ and 10 in total were identified as target lesions (TLs) and recorded at baseline. TLs should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements either by imaging or clinically. A sum of the longest diameter for all TLs was calculated as baseline sum longest diameter (SLD). All other lesions (or sites of disease) should be identified as non-TLs and recorded at baseline. PD for TLs was defined as greater than or equal to (\geq) 20 percent (%) increase in SLD, taking as reference smallest SLD recorded since treatment started or appearance of 1 or more new lesions. PD for non-TLs was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. Percentage of Participants with PD by IRC or death from any cause was reported. | |
| End point type | Primary |
| End point timeframe: From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months) | |

Notes:

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

Justification: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|-----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 ^[2] | 496 ^[3] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 53.5 | 61.3 | | |

Notes:

[2] - Intent-to-treat (ITT) population: all randomized participants on the basis of treatment assigned.

[3] - ITT population: all randomized participants on the basis of the treatment assigned at randomization.

Statistical analyses

Primary: Progression-free Survival (PFS) as Assessed by an IRC (Co-primary Endpoint)

| | |
|---|---|
| End point title | Progression-free Survival (PFS) as Assessed by an IRC (Co-primary Endpoint) |
| End point description: | |
| Tumor response was assessed by an IRC according to modified RECIST. All measurable lesions up to a maximum of 5 per organ and 10 in total were identified as TLs (on the basis of their size and their suitability for accurate repeated measurements either by imaging or clinically) and recorded at baseline. A sum of the longest diameter for all TLs was calculated as baseline SLD. All other lesions were identified as non-TLs and recorded at baseline. PD for TLs: $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or appearance of 1 or more new lesions. PD for non-TLs: appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. PFS: time from randomization to first documented PD by IRC or death from any cause (whichever occurred earlier). The median duration of PFS was estimated using Kaplan-Meier method. The 95% confidence interval (CI) was computed using the method of Brookmeyer and Crowley. ITT population. | |
| End point type | Primary |
| End point timeframe: | |
| From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months) | |

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9.6 (8.25 to 10.64) | 6.4 (5.68 to 7.06) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or greater than [$>$] 1), and visceral/ non-visceral disease. Hazard ratio (HR) (relative to Lapatinib + Capecitabine) was estimated by Cox regression. | |
| Comparison groups | Trastuzumab Emtansine v Lapatinib + Capecitabine |
| Number of subjects included in analysis | 991 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.549 |
| upper limit | 0.771 |

Primary: Percentage of Participants Who Died: Second Interim Analysis

| | |
|-----------------|---|
| End point title | Percentage of Participants Who Died: Second Interim |
|-----------------|---|

End point description:

The percentage of participants who died from any cause was reported. The results are reported from second interim analysis, which deemed to be the confirmatory. ITT population.

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

End point timeframe:

From the date of randomization through the data cut-off date of 31 Jul 2012 (up to 3 years, 5 months)

Notes:

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

Justification: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|-----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 30.1 | 36.7 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival: Second Interim Analysis (Co-primary Endpoint)

| | |
|-----------------|---|
| End point title | Overall Survival: Second Interim Analysis (Co-primary Endpoint) |
|-----------------|---|

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. The median duration of OS was estimated using Kaplan-Meier method. The 95% CI was computed using the method of Brookmeyer and Crowley. The results are reported from second interim analysis, which deemed to be the confirmatory. ITT population.

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

End point timeframe:

From the date of randomization through the data cut-off date of 31 Jul 2012 (up to 3 years, 5 months)

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 30.9 (26.81 to 34.27) | 25.1 (22.74 to 27.96) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. HR (relative to Lapatinib + Capecitabine) was estimated by Cox regression. | |
| Comparison groups | Trastuzumab Emtansine v Lapatinib + Capecitabine |
| Number of subjects included in analysis | 991 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0006 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.682 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.548 |
| upper limit | 0.849 |

Primary: Percentage of Participants Who Died: Final Analysis

| | |
|---|--|
| End point title | Percentage of Participants Who Died: Final Analysis ^[5] |
| End point description: | |
| The percentage of participants who died from any cause was reported. The results reported are from the final analysis. The final analysis is descriptive. ITT Population. | |
| End point type | Primary |
| End point timeframe: | |
| From the date of randomization through the data cut-off date of 31 Dec 2014 (up to 5 years, 11 months) | |

Notes:

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

Justification: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

| | | | | |
|-----------------------------------|-----------------------|--------------------------|--|--|
| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 61.2 | 67.1 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival: Final Analysis

| | |
|-----------------|----------------------------------|
| End point title | Overall Survival: Final Analysis |
|-----------------|----------------------------------|

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. The median duration of OS was estimated using Kaplan-Meier method. The 95% CI was computed using the method of Brookmeyer and Crowley. The results reported are from the final analysis. The final analysis is descriptive. ITT Population.

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

End point timeframe:

From the date of randomization through the data cut-off date of 31 Dec 2014 (up to 5 years, 11 months)

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|-----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 29.9 (26.32 to 34.1) | 25.9 (22.74 to 28.32) | | |

Statistical analyses

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

Statistical analysis description:

Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. HR (relative to Lapatinib + Capecitabine) was estimated by Cox regression.

| | |
|-------------------|--|
| Comparison groups | Trastuzumab Emtansine v Lapatinib + Capecitabine |
|-------------------|--|

| | |
|---|-----|
| Number of subjects included in analysis | 991 |
|---|-----|

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

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

| | |
|---------|----------|
| P-value | = 0.0003 |
|---------|----------|

| | |
|--------|---------|
| Method | Logrank |
|--------|---------|

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

| | |
|----------------|-------|
| Point estimate | 0.749 |
|----------------|-------|

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.639 |
| upper limit | 0.877 |

Primary: Percentage of Participants Who Were Alive at Year 1

| | |
|-----------------|--|
| End point title | Percentage of Participants Who Were Alive at Year 1 ^[6] |
|-----------------|--|

End point description:

1 year survival was defined as the percentage of participants alive 1 year after starting treatment. The results reported are from the final analysis. ITT population.

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

End point timeframe:

Year 1

Notes:

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

Justification: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|-----------------------------------|--------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 85.3 (82.15 to 88.54) | 78.9 (75.19 to 82.65) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Were Alive at Year 2

| | |
|-----------------|--|
| End point title | Percentage of Participants Who Were Alive at Year 2 ^[7] |
|-----------------|--|

End point description:

2 year survival was defined as the percentage of participants alive 2 years after starting treatment. The results reported are from the final analysis. ITT Population.

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

End point timeframe:

Year 2

Notes:

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

Justification: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|-----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 59.6 (55.1 to 64.06) | 52.4 (47.81 to 57.08) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With PD or Death as Assessed by the Investigator

| | |
|-----------------|---|
| End point title | Percentage of Participants With PD or Death as Assessed by the Investigator |
|-----------------|---|

End point description:

PD was assessed by the investigator using modified RECIST. All measurable lesions up to a maximum of 5 per organ and 10 in total were identified as TLs and recorded at baseline. A sum of the longest diameter for all TLs was calculated as baseline SLD. PD for TLs was defined as $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or the appearance of 1 or more new lesions. PD for non-TLs was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. The percentage of participants who died or experienced PD by Investigator was reported. ITT population.

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

End point timeframe:

From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|-----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 58 | 67.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Assessed by the Investigator

| | |
|-----------------|-------------------------------------|
| End point title | PFS as Assessed by the Investigator |
|-----------------|-------------------------------------|

End point description:

Tumor response was assessed by the investigator according to modified RECIST. All measurable lesions up to a maximum of 5 per organ and 10 in total were identified as TLs and recorded at baseline. A sum of the longest diameter for all TLs was calculated as baseline SLD. PD for TLs was defined as $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or the appearance of 1 or more new lesions. PD for non-TLs was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. PFS was defined as the time from randomization to first documented PD by Investigator or death from any cause (whichever occurred

earlier). The median duration of PFS was estimated using Kaplan-Meier method. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT population.

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

End point timeframe:

From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9.4 (7.49 to 10.78) | 5.8 (5.59 to 6.93) | | |

Statistical analyses

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

Statistical analysis description:

Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. HR (relative to Lapatinib + Capecitabine) was estimated by Cox regression.

| | |
|---|--|
| Comparison groups | Trastuzumab Emtansine v Lapatinib + Capecitabine |
| Number of subjects included in analysis | 991 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.658 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 0.774 |

Secondary: Percentage of Participants With Objective Response (OR) as Assessed by an IRC

| | |
|-----------------|---|
| End point title | Percentage of Participants With Objective Response (OR) as Assessed by an IRC |
|-----------------|---|

End point description:

Tumor response was assessed by an IRC according to modified RECIST. OR was defined as the percentage of participants with a complete response (CR) or partial response (PR). All measurable lesions up to a maximum of 5 per organ and 10 in total were identified as TLs and recorded at baseline. A sum of the longest diameter for all TLs was calculated as baseline SLD. For TLs, a CR was defined as the disappearance of all TLs and a PR was defined as $\geq 30\%$ decrease in the SLD of TLs, taking as reference the baseline SLD. For non-TLs, a CR was defined as the disappearance of all non-TLs and a PR was defined as the persistence of 1 or more non-TLs. Confirmation of response at a consecutive tumor assessment at least 4 weeks apart was required. Participants without a post-baseline tumor assessment

were considered non-responders. The percentage of participants with CR or PR by IRC was reported. The 95% CI was computed using Blyth-Still Casella exact CI method. ITT population.

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

End point timeframe:

From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|-----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 397 ^[8] | 389 ^[9] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 43.6 (38.6 to 48.6) | 30.8 (26.3 to 35.7) | | |

Notes:

[8] - Only participants with measurable disease at baseline were included in the analysis.

[9] - Only participants with measurable disease at baseline were included in the analysis.

Statistical analyses

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

Statistical analysis description:

Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. The 95% CI for the difference in objective response rate (Trastuzumab emtansine minus Lapatinib + Capecitabine) was computed by using the approximate normal method.

| | |
|---|--|
| Comparison groups | Trastuzumab Emtansine v Lapatinib + Capecitabine |
| Number of subjects included in analysis | 786 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 |
| Method | Mantel-Haenszel chi-squared test |
| Parameter estimate | Difference in Objective Response Rates |
| Point estimate | 12.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6 |
| upper limit | 19.4 |

Secondary: Duration of Objective Response (DOR) as Assessed by an IRC

| | |
|-----------------|--|
| End point title | Duration of Objective Response (DOR) as Assessed by an IRC |
|-----------------|--|

End point description:

Tumor response was assessed by an IRC according to modified RECIST. DOR was defined as the time from first documented OR to first documented PD or death from any cause, whichever occurred earlier. OR was defined as a CR or PR determined on 2 consecutive tumor assessments at least 4 weeks apart. For TLs, CR was defined as the disappearance of all TLs; PR was defined as $\geq 30\%$ decrease in the SLD of TLs, taking as reference the baseline SLD; and PD was defined as $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or the appearance of 1 or more new lesions. For non-TLs, CR was defined as the disappearance of all non-TLs; PR was defined as the persistence of 1 or more non-TLs; and PD was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT population.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months) | |

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 173 ^[10] | 120 ^[11] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 12.6 (8.38 to 20.76) | 6.5 (5.45 to 7.16) | | |

Notes:

[10] - Only participants with an objective response were included in the analysis.

[11] - Only participants with an objective response were included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Benefit as Assessed by the IRC

| | |
|-----------------|---|
| End point title | Percentage of Participants With Clinical Benefit as Assessed by the IRC |
|-----------------|---|

End point description:

Tumor response was assessed by an IRC according to modified RECIST. Participants were considered as experienced clinical benefit if they had an OR or maintained stable disease (SD) for at least 6 months from randomization. OR: CR or PR determined on 2 consecutive tumor assessments ≥ 4 weeks apart. For TLs, CR: disappearance of all TLs; PR: $\geq 30\%$ decrease in the SLD of TLs, taking as reference the baseline SLD; PD: $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or appearance of 1 or more new lesions; and SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. For non-TLs, CR: disappearance of all non-TLs; PR/SD: persistence of 1 or more non-TLs; and PD: appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. Participants without a post-baseline tumor assessment were considered non-responders. The 95% CI was computed using Blyth-Still Casella exact CI method.

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

End point timeframe:

From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months)

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|-----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 397 ^[12] | 389 ^[13] | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 58.2 (53.3 to 63.1) | 44.2 (39.2 to 49.2) | | |

Notes:

[12] - ITT population. Only participants with measurable disease at Baseline were included in the analysis.

[13] - ITT population. Only participants with measurable disease at Baseline were included in the analysis.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: The 95% CI for the difference in clinical benefit rate (Trastuzumab emtansine minus Lapatinib + Capecitabine) was computed by using the normal approximation method. | |
| Comparison groups | Trastuzumab Emtansine v Lapatinib + Capecitabine |
| Number of subjects included in analysis | 786 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Difference in Clinical Benefit Rate |
| Point estimate | 14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7 |
| upper limit | 20.9 |

Secondary: Percentage of Participants With Treatment Failure

| | |
|---|---|
| End point title | Percentage of Participants With Treatment Failure |
| End point description: Treatment failure was defined as discontinuation of treatment for any reason, including PD (per investigator review), treatment toxicity, or death from any cause. For "Lapatinib + Capecitabine" arm, a participant was considered as treatment failure only if both drugs were discontinued. For TLs, PD was defined as $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or the appearance of 1 or more new lesions. For non-TLs, PD was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. Percentage of participants with treatment failure was reported. ITT population. | |
| End point type | Secondary |
| End point timeframe: From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months) | |

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|-----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 63.2 | 74.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

| | |
|---|---------------------------|
| End point title | Time to Treatment Failure |
| End point description: Time to treatment failure was defined as the time from randomization to discontinuation of treatment for any reason, including PD (per investigator review), treatment toxicity, or death from any cause. For | |

"Lapatinib + Capecitabine" arm, a participant was considered as treatment failure only if both drugs were discontinued with treatment failure date as the later of the 2 discontinuation dates. For TLs, PD was defined as $\geq 20\%$ increase in the SLD, taking as reference the smallest SLD recorded since treatment started or the appearance of 1 or more new lesions. For non-TLs, PD was defined as appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. The median time to treatment failure was estimated using Kaplan-Meier method. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT population.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months) | |

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 495 | 496 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.9 (6.41 to 9) | 5.8 (5.52 to 6.31) | | |

Statistical analyses

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

Statistical analysis description:

Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. HR (relative to Lapatinib + Capecitabine) was estimated by Cox regression.

| | |
|---|--|
| Comparison groups | Trastuzumab Emtansine v Lapatinib + Capecitabine |
| Number of subjects included in analysis | 991 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.703 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.602 |
| upper limit | 0.82 |

Secondary: Percentage of Participants With Symptom Progression

| | |
|-----------------|---|
| End point title | Percentage of Participants With Symptom Progression |
|-----------------|---|

End point description:

Symptom progression was defined as the documentation of a ≥ 5 -point decrease from baseline in the scoring of responses as measured by the Functional Assessment of Cancer Therapy-for participants with Breast Cancer (FACT-B) questionnaire with the Trial Outcomes Index-Physical/Functional/Breast (TOI-PFB) subscale. The FACT-B TOI-PFB subscale contained 24 items from 3 subsections of the FACT-B questionnaire: Physical well-being, functional well-being, and additional concerns for breast cancer

participants (breast cancer subscale [BCS]). All items in the questionnaire were rated by the participant on a 5-point scale ranging from 0 ("not at all") to 4 ("very much"). The total score ranged from 0 to 96 with higher score indicating better perceived quality of life. The percentage of participants with symptom progression was reported. ITT population. Only female participants with a Baseline assessment and at least 1 follow-up assessment were included in the analysis.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months) | |

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|-----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 450 | 445 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 54.7 | 57.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptom Progression

| | |
|---|-----------------------------|
| End point title | Time to Symptom Progression |
| End point description: | |
| Time to symptom progression was defined as the time from randomization to the first documentation of a ≥ 5 -point decrease from baseline in the scoring of responses as measured by the FACT-B questionnaire with the TOI-PFB subscale. The FACT-B TOI-PFB subscale contained 24 items from 3 subsections of the FACT-B questionnaire: Physical well-being, functional well-being, and additional concerns for breast cancer participants (BCS). All items in the questionnaire were rated by the participant on a 5-point scale ranging from 0 ("not at all") to 4 ("very much"). The total score ranged from 0 to 96 with higher score indicating better perceived quality of life. The median time to symptom progression was estimated using Kaplan-Meier method. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT population. Only female participants with a Baseline assessment and at least 1 follow-up assessment were included in the analysis. | |
| End point type | Secondary |
| End point timeframe: | |
| From the date of randomization through the data cut-off date of 14 Jan 2012 (up to 2 years, 11 months) | |

| End point values | Trastuzumab Emtansine | Lapatinib + Capecitabine | | |
|----------------------------------|-----------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 450 | 445 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.1 (5.59 to 8.44) | 4.6 (4.14 to 5.78) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: Analysis stratified by region of enrollment, number of prior chemotherapeutic regimens (0-1 or >1), and visceral/ non-visceral disease. HR (relative to Lapatinib + Capecitabine) was estimated by Cox regression. | |
| Comparison groups | Trastuzumab Emtansine v Lapatinib + Capecitabine |
| Number of subjects included in analysis | 895 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0121 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.796 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.667 |
| upper limit | 0.951 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study-related SAEs were reported from randomization to first treatment; all SAEs/non-SAEs from start of treatment until 30 days after treatment; and thereafter treatment related SAEs until data cut-off date of 21-Sep-2015 (up to 6 years and 7 months)

Adverse event reporting additional description:

Safety population included participants who received at least 1 dose of study medication. Safety analyses were based on the actual treatment received. For participants who crossed over from lapatinib + capecitabine to trastuzumab emtansine, data is reported from time of cross-over until 21-Sep-2015 (up to 3 years and 2 months).

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Trastuzumab Emtansine |
|-----------------------|-----------------------|

Reporting group description:

Participants received trastuzumab emtansine 3.6 mg/kg IV infusion over 30-90 minutes on Day 1 of each 21-day treatment cycle until PD (as assessed by the investigator), unmanageable toxicity, or study termination.

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

Reporting group description:

Participants received lapatinib 1250 mg (five 250 mg tablets) orally once daily during each 21-day cycle + capecitabine 1000 mg/m² orally twice daily on Days 1-14 of each 21-day treatment cycle until PD (as assessed by the investigator), unmanageable toxicity, or study termination. Participants of this group were allowed to cross over to receive trastuzumab emtansine based on statistically significant OS benefit in favor of trastuzumab emtansine demonstrated in second interim analysis.

| | |
|-----------------------|---|
| Reporting group title | Lapatinib + Capecitabine/ Trastuzumab Emtansine |
|-----------------------|---|

Reporting group description:

Participants of "Lapatinib + Capecitabine" arm were allowed to cross over to receive trastuzumab emtansine based on statistically significant OS benefit in favor of trastuzumab emtansine demonstrated in second interim analysis.

| Serious adverse events | Trastuzumab Emtansine | Lapatinib + Capecitabine | Lapatinib + Capecitabine/ Trastuzumab Emtansine |
|---|-----------------------|--------------------------|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 92 / 490 (18.78%) | 99 / 488 (20.29%) | 19 / 136 (13.97%) |
| number of deaths (all causes) | 305 | 277 | 55 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Infected neoplasm | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Second primary malignancy | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine cancer | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lentigo maligna | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Labile blood pressure | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 2 / 488 (0.41%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 490 (1.63%) | 3 / 488 (0.61%) | 2 / 136 (1.47%) |
| occurrences causally related to treatment / all | 5 / 9 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Menometrorrhagia | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metrorrhagia | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Alveolitis allergic | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Hypoxia | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 9 / 488 (1.84%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Agitation | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Substance-induced psychotic disorder | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delayed haemolytic transfusion reaction | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Extradural haematoma | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 3 / 490 (0.61%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovial rupture | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound secretion | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiomyopathy | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coma | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Dizziness | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 490 (0.41%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Metabolic encephalopathy | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Parkinson's disease | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 490 (0.00%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia of malignant disease | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 490 (0.82%) | 1 / 488 (0.20%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 6 / 7 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Macular hole | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|------------------|-----------------|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 490 (0.82%) | 3 / 488 (0.61%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 490 (0.61%) | 17 / 488 (3.48%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 19 / 19 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula of small intestine | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 490 (0.41%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 3 / 488 (0.61%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peptic ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed | 7 / 490 (1.43%) | 10 / 488 (2.05%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 3 / 7 | 9 / 11 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis toxic | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Portal hypertension | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nodular regenerative hyperplasia | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis contact | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin haemorrhage | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ureteric obstruction | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 490 (0.61%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal column stenosis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spondylitis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 3 / 488 (0.61%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 490 (0.20%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| H1N1 influenza | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Listeriosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Parotitis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 490 (0.82%) | 1 / 488 (0.20%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Salmonellosis | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 490 (0.61%) | 0 / 488 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 2 / 136 (1.47%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Unmapped (Bacteremia due to infected port) | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 2 / 488 (0.41%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 490 (0.20%) | 0 / 488 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 1 / 488 (0.20%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Trastuzumab Emtansine | Lapatinib + Capecitabine | Lapatinib + Capecitabine/ Trastuzumab Emtansine |
|---|----------------------------------|-------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 474 / 490 (96.73%) | 471 / 488 (96.52%) | 115 / 136 (84.56%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 29 / 490 (5.92%) | 11 / 488 (2.25%) | 7 / 136 (5.15%) |
| occurrences (all) | 40 | 13 | 13 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 91 / 490 (18.57%) | 86 / 488 (17.62%) | 23 / 136 (16.91%) |
| occurrences (all) | 230 | 186 | 47 |
| Chest pain | | | |
| subjects affected / exposed | 40 / 490 (8.16%) | 27 / 488 (5.53%) | 0 / 136 (0.00%) |
| occurrences (all) | 50 | 30 | 0 |
| Chills | | | |
| subjects affected / exposed | 42 / 490 (8.57%) | 16 / 488 (3.28%) | 13 / 136 (9.56%) |
| occurrences (all) | 59 | 20 | 19 |
| Fatigue | | | |
| subjects affected / exposed | 180 / 490 (36.73%) | 145 / 488 (29.71%) | 30 / 136 (22.06%) |
| occurrences (all) | 360 | 259 | 65 |
| Influenza like illness | | | |
| subjects affected / exposed | 26 / 490 (5.31%) | 9 / 488 (1.84%) | 13 / 136 (9.56%) |
| occurrences (all) | 36 | 11 | 41 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 33 / 490 (6.73%) | 93 / 488 (19.06%) | 0 / 136 (0.00%) |
| occurrences (all) | 65 | 172 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 38 / 490 (7.76%) | 38 / 488 (7.79%) | 10 / 136 (7.35%) |
| occurrences (all) | 49 | 47 | 11 |
| Pain | | | |
| subjects affected / exposed | 35 / 490 (7.14%) | 14 / 488 (2.87%) | 0 / 136 (0.00%) |
| occurrences (all) | 43 | 14 | 0 |
| Pyrexia | | | |

| | | | |
|--|--------------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 95 / 490 (19.39%) 165 | 43 / 488 (8.81%) 54 | 18 / 136 (13.24%) 25 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 100 / 490 (20.41%) | 68 / 488 (13.93%) | 18 / 136 (13.24%) |
| occurrences (all) | 148 | 80 | 27 |
| Dyspnoea | | | |
| subjects affected / exposed | 61 / 490 (12.45%) | 41 / 488 (8.40%) | 17 / 136 (12.50%) |
| occurrences (all) | 72 | 55 | 25 |
| Epistaxis | | | |
| subjects affected / exposed | 121 / 490 (24.69%) | 44 / 488 (9.02%) | 35 / 136 (25.74%) |
| occurrences (all) | 235 | 55 | 85 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 24 / 490 (4.90%) | 26 / 488 (5.33%) | 0 / 136 (0.00%) |
| occurrences (all) | 29 | 32 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 11 / 136 (8.09%) |
| occurrences (all) | 0 | 0 | 17 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 31 / 490 (6.33%) | 15 / 488 (3.07%) | 0 / 136 (0.00%) |
| occurrences (all) | 38 | 17 | 0 |
| Depression | | | |
| subjects affected / exposed | 27 / 490 (5.51%) | 30 / 488 (6.15%) | 0 / 136 (0.00%) |
| occurrences (all) | 31 | 33 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 69 / 490 (14.08%) | 45 / 488 (9.22%) | 14 / 136 (10.29%) |
| occurrences (all) | 86 | 54 | 19 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 92 / 490 (18.78%) | 48 / 488 (9.84%) | 14 / 136 (10.29%) |
| occurrences (all) | 285 | 79 | 22 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 123 / 490 (25.10%) | 53 / 488 (10.86%) | 25 / 136 (18.38%) |
| occurrences (all) | 376 | 96 | 56 |
| Blood alkaline phosphatase increased | | | |

| | | | |
|---|---------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 26 / 490 (5.31%) 59 | 23 / 488 (4.71%) 25 | 9 / 136 (6.62%) 12 |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 21 / 490 (4.29%) 45 | 32 / 488 (6.56%) 83 | 11 / 136 (8.09%) 32 |
| Weight decreased subjects affected / exposed occurrences (all) | 38 / 490 (7.76%) 55 | 37 / 488 (7.58%) 45 | 7 / 136 (5.15%) 10 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 0 / 490 (0.00%) 0 | 0 / 488 (0.00%) 0 | 8 / 136 (5.88%) 16 |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 0 / 490 (0.00%) 0 | 0 / 488 (0.00%) 0 | 8 / 136 (5.88%) 9 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 62 / 490 (12.65%) 88 | 50 / 488 (10.25%) 75 | 0 / 136 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 41 / 490 (8.37%) 44 | 21 / 488 (4.30%) 27 | 0 / 136 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 146 / 490 (29.80%) 257 | 77 / 488 (15.78%) 95 | 28 / 136 (20.59%) 79 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 59 / 490 (12.04%) 106 | 30 / 488 (6.15%) 38 | 16 / 136 (11.76%) 20 |
| Paraesthesia subjects affected / exposed occurrences (all) | 31 / 490 (6.33%) 40 | 20 / 488 (4.10%) 33 | 7 / 136 (5.15%) 11 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 36 / 490 (7.35%) 81 | 27 / 488 (5.53%) 34 | 0 / 136 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|-----------------------------|--------------------|--------------------|-------------------|
| Anaemia | | | |
| subjects affected / exposed | 67 / 490 (13.67%) | 40 / 488 (8.20%) | 11 / 136 (8.09%) |
| occurrences (all) | 169 | 87 | 24 |
| Neutropenia | | | |
| subjects affected / exposed | 37 / 490 (7.55%) | 43 / 488 (8.81%) | 0 / 136 (0.00%) |
| occurrences (all) | 144 | 100 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 150 / 490 (30.61%) | 13 / 488 (2.66%) | 23 / 136 (16.91%) |
| occurrences (all) | 574 | 26 | 60 |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 7 / 136 (5.15%) |
| occurrences (all) | 0 | 0 | 8 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 43 / 490 (8.78%) | 50 / 488 (10.25%) | 0 / 136 (0.00%) |
| occurrences (all) | 62 | 75 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 60 / 490 (12.24%) | 45 / 488 (9.22%) | 0 / 136 (0.00%) |
| occurrences (all) | 69 | 69 | 0 |
| Constipation | | | |
| subjects affected / exposed | 139 / 490 (28.37%) | 59 / 488 (12.09%) | 22 / 136 (16.18%) |
| occurrences (all) | 204 | 75 | 30 |
| Diarrhoea | | | |
| subjects affected / exposed | 123 / 490 (25.10%) | 385 / 488 (78.89%) | 20 / 136 (14.71%) |
| occurrences (all) | 192 | 1254 | 58 |
| Dry mouth | | | |
| subjects affected / exposed | 85 / 490 (17.35%) | 26 / 488 (5.33%) | 20 / 136 (14.71%) |
| occurrences (all) | 115 | 30 | 29 |
| Dyspepsia | | | |
| subjects affected / exposed | 51 / 490 (10.41%) | 57 / 488 (11.68%) | 7 / 136 (5.15%) |
| occurrences (all) | 67 | 71 | 7 |
| Gingival bleeding | | | |
| subjects affected / exposed | 0 / 490 (0.00%) | 0 / 488 (0.00%) | 8 / 136 (5.88%) |
| occurrences (all) | 0 | 0 | 11 |
| Nausea | | | |

| | | | |
|--|---------------------------|---------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 203 / 490 (41.43%) 487 | 224 / 488 (45.90%) 431 | 35 / 136 (25.74%) 70 |
| Stomatitis subjects affected / exposed occurrences (all) | 20 / 490 (4.08%) 22 | 70 / 488 (14.34%) 103 | 0 / 136 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 98 / 490 (20.00%) 167 | 145 / 488 (29.71%) 250 | 13 / 136 (9.56%) 25 |
| Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 13 / 490 (2.65%) 31 | 46 / 488 (9.43%) 99 | 0 / 136 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 19 / 490 (3.88%) 25 | 25 / 488 (5.12%) 27 | 0 / 136 (0.00%) 0 |
| Dry skin subjects affected / exposed occurrences (all) | 17 / 490 (3.47%) 24 | 54 / 488 (11.07%) 67 | 8 / 136 (5.88%) 11 |
| Erythema subjects affected / exposed occurrences (all) | 16 / 490 (3.27%) 19 | 25 / 488 (5.12%) 41 | 0 / 136 (0.00%) 0 |
| Nail disorder subjects affected / exposed occurrences (all) | 18 / 490 (3.67%) 22 | 48 / 488 (9.84%) 67 | 0 / 136 (0.00%) 0 |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 3 / 490 (0.61%) 3 | 28 / 488 (5.74%) 51 | 0 / 136 (0.00%) 0 |
| Palmar–plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all) | 7 / 490 (1.43%) 8 | 291 / 488 (59.63%) 927 | 7 / 136 (5.15%) 7 |
| Pruritus subjects affected / exposed occurrences (all) | 32 / 490 (6.53%) 44 | 46 / 488 (9.43%) 58 | 7 / 136 (5.15%) 9 |
| Rash | | | |

| | | | |
|---|--------------------|--------------------|-------------------|
| subjects affected / exposed | 64 / 490 (13.06%) | 133 / 488 (27.25%) | 17 / 136 (12.50%) |
| occurrences (all) | 102 | 223 | 24 |
| Skin fissures | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 27 / 488 (5.53%) | 0 / 136 (0.00%) |
| occurrences (all) | 3 | 67 | 0 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 2 / 490 (0.41%) | 25 / 488 (5.12%) | 0 / 136 (0.00%) |
| occurrences (all) | 2 | 33 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 102 / 490 (20.82%) | 46 / 488 (9.43%) | 21 / 136 (15.44%) |
| occurrences (all) | 150 | 56 | 28 |
| Back pain | | | |
| subjects affected / exposed | 78 / 490 (15.92%) | 63 / 488 (12.91%) | 9 / 136 (6.62%) |
| occurrences (all) | 110 | 80 | 12 |
| Bone pain | | | |
| subjects affected / exposed | 34 / 490 (6.94%) | 20 / 488 (4.10%) | 0 / 136 (0.00%) |
| occurrences (all) | 39 | 33 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 39 / 490 (7.96%) | 22 / 488 (4.51%) | 8 / 136 (5.88%) |
| occurrences (all) | 53 | 25 | 13 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 46 / 490 (9.39%) | 22 / 488 (4.51%) | 10 / 136 (7.35%) |
| occurrences (all) | 58 | 27 | 11 |
| Myalgia | | | |
| subjects affected / exposed | 70 / 490 (14.29%) | 20 / 488 (4.10%) | 16 / 136 (11.76%) |
| occurrences (all) | 120 | 31 | 23 |
| Pain in extremity | | | |
| subjects affected / exposed | 71 / 490 (14.49%) | 61 / 488 (12.50%) | 8 / 136 (5.88%) |
| occurrences (all) | 99 | 84 | 8 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 50 / 490 (10.20%) | 41 / 488 (8.40%) | 14 / 136 (10.29%) |
| occurrences (all) | 78 | 56 | 22 |
| Paronychia | | | |

| | | | |
|---|---------------------------|---------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 2 / 490 (0.41%) 3 | 59 / 488 (12.09%) 181 | 0 / 136 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 56 / 490 (11.43%) 92 | 40 / 488 (8.20%) 49 | 14 / 136 (10.29%) 22 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 52 / 490 (10.61%) 75 | 21 / 488 (4.30%) 25 | 0 / 136 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 105 / 490 (21.43%) 149 | 117 / 488 (23.98%) 170 | 21 / 136 (15.44%) 26 |
| Dehydration subjects affected / exposed occurrences (all) | 9 / 490 (1.84%) 10 | 25 / 488 (5.12%) 37 | 0 / 136 (0.00%) 0 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 47 / 490 (9.59%) 89 | 45 / 488 (9.22%) 82 | 7 / 136 (5.15%) 11 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 19 February 2010 | Two interim analyses of the secondary efficacy endpoint OS were specified at the request of the Data Monitoring Committee. No interim analysis of the primary endpoint of PFS was included. The use of echocardiogram (ECHO) rather than multi-gated acquisition (MUGA) scans was recommended for the evaluation of cardiac function because of the anticipated shortage of technetium-99 (Tc99). Bone scans (skeletal X-rays) were included at the screening visit and as part of subsequent tumor assessments. |
| 13 May 2010 | All revisions planned for Protocol Amendment 1 were carried forward to Protocol Amendment 2, with the exception of one of the two proposed interim analyses of OS. Based on regulatory feedback, the interim analysis planned after 125 deaths, was considered to be premature and was therefore not included. The definition of PFS was updated per the United States Food and Drug Administration (US FDA) Guidance Documents regarding endpoints for oncology clinical trials to include all deaths, inclusive of deaths that occurred beyond 30 days after the last dose of study treatment. |
| 04 October 2010 | Overall survival was changed from a secondary endpoint to a co-primary endpoint to ensure more robust trial results. Further, the sample size was increased from 580 to 980 participants to ensure the study was properly powered to detect a clinically meaningful OS benefit. The number of participants in the pharmacokinetic analysis was increased from 80 to 160 participants. The frequency of the urine pregnancy test for females of childbearing potential was increased to every three cycles because of the study drugs' potential to cause harm to a fetus. The frequency of administration of the FACT-B questionnaire was increased to obtain a more accurate assessment of the changes in symptom burden due to disease progression. |
| 30 May 2012 | As per Protocol Amendment 4, eligible participants randomized to the lapatinib plus capecitabine arm could cross over to receive trastuzumab emtansine if a statistically significant OS benefit in favor of trastuzumab emtansine were demonstrated. |
| 22 February 2013 | Allowed participants in both treatment arms who developed progression in the brain but demonstrated control of their systemic and visceral disease to continue to receive treatment. Included the possibility of post-trial access to trastuzumab emtansine treatment through an extension study. Updates to safety wording were made in alignment with current recommendations. |
| 08 August 2014 | The end of study definition was updated to specify that this will occur when the last participant has completed the Study Drug Completion Visit. Updates to safety wording were made in alignment with current recommendations. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported