



Clinical trial results:

A Phase II Study of Lapatinib for Brain Metastases in Subjects with ErbB2-Positive Breast Cancer Following Trastuzumab-based Systemic Therapy and Cranial Radiotherapy

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2005-003944-68 |
| Trial protocol | SE AT DE GB BE ES GR IT |
| Global end of trial date | 15 March 2018 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 30 March 2019 |
| First version publication date | 30 March 2019 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | EGF105084 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00263588 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Novartis: CLAP016A2202 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Study Lead, Novartis Pharma AG, 41 +613241111, novartis.email@novartis.com |
| Scientific contact | Study Director, Novartis Pharma AG, 41 +613241111, novartis.email@novartis.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 11 March 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 March 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Determine central nervous system (CNS) objective response rate to lapatinib monotherapy in subjects with progressive brain metastases from human epidermal growth factor receptor 2 (HER2/ErbB2)-overexpressing breast cancer

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 02 December 2005 |
| 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 | Austria: 8 |
| Country: Number of subjects enrolled | Belgium: 10 |
| Country: Number of subjects enrolled | Canada: 7 |
| Country: Number of subjects enrolled | France: 26 |
| Country: Number of subjects enrolled | Germany: 18 |
| Country: Number of subjects enrolled | Greece: 10 |
| Country: Number of subjects enrolled | Australia: 18 |
| Country: Number of subjects enrolled | India: 2 |
| Country: Number of subjects enrolled | Italy: 9 |
| Country: Number of subjects enrolled | Japan: 6 |
| Country: Number of subjects enrolled | Poland: 4 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | Sweden: 4 |
| Country: Number of subjects enrolled | Switzerland: 5 |
| Country: Number of subjects enrolled | Taiwan: 5 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | United States: 92 |
| Worldwide total number of subjects | 242 |
| EEA total number of subjects | 107 |

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) | 220 |
| From 65 to 84 years | 21 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

The Intent-to-Treat (ITT) Population: all subjects who received at least one dose of study medication

Modified ITT (MITT) Population: all subjects who received at least four doses (750 mg lapatinib twice daily for two days) of study medication and who had measurable brain metastases (≥ 1 cm in diameter) at baseline assessment

Pre-assignment

Screening details:

Main phase: ITT 95 in Cohort A, 147 in Cohort B. MITT, 94 in Cohort A, and 143 subjects in Cohort B
Optional open-label extension phase: 51 subjects. Long-term follow up (LTFU) Protocol amendment added on 15-Apr-2013

Period 1

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

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort A |

Arm description:

750mg lapatinib administered orally twice daily. Cohort A subjects had Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and one or two prior trastuzumab-containing regimens, in total, for treatment of breast cancer in adjuvant and/or metastatic settings

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | lapatinib |
| Investigational medicinal product code | EGF105 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Cohort A subjects had Eastern Cooperative Oncology Group (ECOG) performance status 0-1

| | |
|------------------|----------|
| Arm title | Cohort B |
|------------------|----------|

Arm description:

750mg lapatinib administered orally twice daily. Cohort B subjects had ECOG performance status 2 or more than 2 prior trastuzumab-containing regimens for treatment of breast cancer in the adjuvant and/or metastatic settings.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | lapatinib |
| Investigational medicinal product code | EGF105 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

750mg lapatinib administered orally twice daily. Cohort B subjects had ECOG performance status 2 or more than 2 prior trastuzumab-containing regimens

| Number of subjects in period 1 | Cohort A | Cohort B |
|---------------------------------------|----------|----------|
| Started | 95 | 147 |
| Completed | 14 | 15 |
| Not completed | 81 | 132 |
| Adverse event, serious fatal | 54 | 90 |
| sponsor terminated study | - | 1 |
| Consent withdrawn by subject | 3 | 4 |
| coma; disease progression; unknown | 10 | 11 |
| Investigator decision | 7 | 15 |
| Lost to follow-up | 7 | 10 |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|---|---------------|-------|--|
| Number of subjects | 242 | 242 | |
| Age, Customized | | | |
| Units: Subjects | | | |
| <18 242 | 0 | 0 | |
| 18-64 years 242 | 220 | 220 | |
| 65-84 years 242 | 21 | 21 | |
| >85 years 242 | 1 | 1 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 49.7 | | |
| standard deviation | ± 10.56 | - | |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 241 | 241 | |
| Male | 1 | 1 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| African American/African | 7 | 7 | |
| American Indian/Alaskan Native | 1 | 1 | |
| Asian – Central/South | 3 | 3 | |
| Asian – Japanese | 6 | 6 | |
| Asian - South-East Asian | 3 | 3 | |
| Asia - East | 5 | 5 | |
| Native Hawaiian or other Pacific Islander | 1 | 1 | |
| White - Arabic/North African | 2 | 2 | |
| White - White/ Caucasian/European | 212 | 212 | |
| Mixed race | 1 | 1 | |
| Other | 1 | 1 | |

Subject analysis sets

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

Subject analysis set description:

The Intent-to-Treat (ITT) Population: all subjects who received at least one dose of study medication

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | MITT |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Modified ITT (MITT) Population: all subjects who received at least four doses (750 mg lapatinib twice daily for two days) of study medication and who had measurable brain metastases (≥1 cm in diameter) at baseline assessment

| Reporting group values | ITT | MITT | |
|---|---------|------|--|
| Number of subjects | 242 | 241 | |
| Age, Customized Units: Subjects | | | |
| <18 242 | 0 | | |
| 18-64 years 242 | 220 | | |
| 65-84 years 242 | 21 | | |
| >85 years 242 | 1 | | |
| Age continuous Units: years | | | |
| arithmetic mean | 49.7 | 0 | |
| standard deviation | ± 10.56 | ± 0 | |
| Sex: Female, Male Units: Subjects | | | |
| Female | 241 | | |
| Male | 1 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| African American/African | 7 | | |
| American Indian/Alaskan Native | 1 | | |
| Asian – Central/South | 3 | | |
| Asian – Japanese | 6 | | |
| Asian - South-East Asian | 3 | | |
| Asia - East | 5 | | |
| Native Hawaiian or other Pacific Islander | 1 | | |
| White - Arabic/North African | 2 | | |
| White - White/ Caucasian/European | 212 | | |
| Mixed race | 1 | | |
| Other | 1 | | |

End points

End points reporting groups

| | |
|--|-----------------------------|
| Reporting group title | Cohort A |
| Reporting group description: 750mg lapatinib administered orally twice daily. Cohort A subjects had Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and one or two prior trastuzumab-containing regimens, in total, for treatment of breast cancer in adjuvant and/or metastatic settings | |
| Reporting group title | Cohort B |
| Reporting group description: 750mg lapatinib administered orally twice daily. Cohort B subjects had ECOG performance status 2 or more than 2 prior trastuzumab-containing regimens for treatment of breast cancer in the adjuvant and/or metastatic settings. | |
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The Intent-to-Treat (ITT) Population: all subjects who received at least one dose of study medication | |
| Subject analysis set title | MITT |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: Modified ITT (MITT) Population: all subjects who received at least four doses (750 mg lapatinib twice daily for two days) of study medication and who had measurable brain metastases (≥ 1 cm in diameter) at baseline assessment | |

Primary: Central nervous system (CNS) objective response rate

| | |
|--|---|
| End point title | Central nervous system (CNS) objective response rate ^[1] |
| End point description: Summary of CNS Objective Response (Lapatinib Monotherapy - MITT Population) Response to lapatinib in patients with progressive brain metastases from ErbB2-overexpressing breast cancer. The primary indicator of drug efficacy was CNS objective response rate. A CNS objective response was defined as either a Complete response (CR) or Partial response (PR), as assessed by volumetric analysis of brain Magnetic resonance imaging (MRI), provided there was no progression of systemic disease outside of the CNS, increasing steroid requirements, or worsening of Neurological signs and symptoms (NSS) A CNS objective response rate was defined as a 50% volumetric reduction in sum of CNS target lesions, with no new or progressive CNS or non-CNS lesions, no increases in tumor-related steroid requirements and no worsening of neurological signs or symptoms | |
| End point type | Primary |
| End point timeframe: time from baseline to data cutoff (25 Sept 2007); approximately 2 years | |

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: No statistical analyses were planned for primary endpoint

| End point values | Cohort A | Cohort B | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 143 | | |
| Units: participants | | | | |
| Complete response (CR) | 0 | 0 | | |
| Partial response (PR) | 6 | 9 | | |
| Stable disease (SD) | 40 | 46 | | |
| Progressive disease (PD) | 40 | 70 | | |
| Unknown | 8 | 18 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Central nervous system (CNS) objective response rate - Response Rate (CR + PR), a percentage

| | |
|-----------------|---|
| End point title | Central nervous system (CNS) objective response rate - Response Rate (CR + PR), a percentage ^[2] |
|-----------------|---|

End point description:

Summary of CNS Objective Response (the Complete Response + Partial Response)

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

End point timeframe:

baseline to time of best response to treatment

Notes:

[2] - 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: No statistical analyses were planned for End Point: Central nervous system (CNS) objective response rate

| End point values | Cohort A | Cohort B | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 143 | | |
| Units: percentage | | | | |
| number (confidence interval 95%) | 6 (2.4 to 13.4) | 6 (2.9 to 11.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Improvement in neurological signs and symptoms (NSS) measured using the Neurological Examination Worksheet

| | |
|-----------------|--|
| End point title | Percentage of Participants with Improvement in neurological signs and symptoms (NSS) measured using the Neurological Examination Worksheet |
|-----------------|--|

End point description:

Physician-reported NSS worksheet is derived from 13 AEs and measured by NCI CTCAE v3.0 grouped into 7 categories: level of consciousness, neurological symptoms, cranial nerves, language, strength, sensation, and ataxia. Improvement of NSS required all of the following: Decrease by 1 or more grades from baseline of any tumor-related NSS, with confirmation at least 4 wks later, No development or worsening in any tumor-related NSS during interval, No radiographic evidence of CNS progression (assessed by volumetric MRI) or systemic (non-CNS) progression (assessed by RECIST) during interval, Stable or decreasing steroids during interval as defined by GSK equivalent doses of an alternative corticosteroid or a dose increase for non-tumor related reasons (e.g., asthma) didn't constitute a steroid increase. Improvement in any non-tumor associated NSS didn't constitute improvement in NSS. Neurological exam, using Neurological Examination Worksheet was assessed at baseline and each 4 weeks

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

End point timeframe:

time from baseline to data cutoff (25 Sept 2007); approximately 2 years

| End point values | ITT | | | |
|--|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 237 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| % with NSS at Baseline | 12.1 (7.9 to 17.5) | | | |
| % with NSS at Baseline with 20% volume reduction | 23.5 (10.7 to 41.2) | | | |
| % w NSS at Baseline & any volume reduction | 23.7 (13.6 to 36.6) | | | |
| % with NSS at Baseline & volume increase of w/drew | 7.2 (3.3 to 13.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a CNS Objective Response or Improvement in Baseline neurological signs and symptoms (NSS)

| | |
|-----------------|---|
| End point title | Percentage of Subjects with a CNS Objective Response or Improvement in Baseline neurological signs and symptoms (NSS) |
|-----------------|---|

End point description:

Summary of Proportion of Subjects with a CNS Objective Response or Improvement in Baseline NSS

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

End point timeframe:

baseline and weeks 8, 16, 24, 32, 40, 48

| End point values | Cohort A | Cohort B | | |
|-----------------------------------|-------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 143 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| week 8 | 23 (14.1 to 33.6) | 14 (7.8 to 21.5) | | |
| week 16 | 2 (0.1 to 12.3) | 8 (2.2 to 19.2) | | |
| week 24 | 8 (0.2 to 38.5) | 11 (1.3 to 33.1) | | |
| week 32 | 17 (0.4 to 64.1) | 0.0 (0.0 to 0.0) | | |
| week 40 | 0.0 (0.0 to 0.0) | 0.0 (0.0 to 0.0) | | |

| | | | | |
|---------|------------------|------------------|--|--|
| week 48 | 0.0 (0.0 to 0.0) | 0.0 (0.0 to 0.0) | | |
|---------|------------------|------------------|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Central Nervous System (CNS) objective response

| | |
|-----------------|---|
| End point title | Duration of Central Nervous System (CNS) objective response |
|-----------------|---|

End point description:

The duration of CNS objective response, defined as the time from first CNS

Objective response until tumor progression at any site or death due to any cause.

A CNS objective response was defined as either a Complete Response (CR) or Partial Response (PR), as assessed by volumetric analysis of magnetic resonance imaging (MRI), provided there was no progression of systemic disease outside of the CNS, increasing steroid requirements, or worsening of tumor-related neurological signs or symptoms.

9.999999999 =upper limit Not evaluable (Due to the low number of CNS responders, a meaningful interpretation of duration of response is not possible). This is only a placeholder

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

End point timeframe:

time from baseline to data cutoff (25 Sept 2007); approximately 2 years

| End point values | Cohort A | Cohort B | | |
|----------------------------------|-----------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 143 | | |
| Units: duration in months | | | | |
| number (confidence interval 95%) | 2.43 (0.99 to 9.9999) | 1.58 (0.99 to 3.55) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with CNS disease control (complete response, partial response or stable disease) at 6 months of lapatinib therapy

| | |
|-----------------|--|
| End point title | Percentage of patients with CNS disease control (complete response, partial response or stable disease) at 6 months of lapatinib therapy |
|-----------------|--|

End point description:

The CNS disease control rate, defined as the percentage of subjects with CR, PR or stable disease at Week 24

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

End point timeframe:
from Start of lapatinib to 6 months

| End point values | Cohort A | Cohort B | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 143 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 9 (3.7 to 16.1) | 2 (0.4 to 6.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP) at any site

| | |
|---|---------------------------------------|
| End point title | Time to progression (TTP) at any site |
| End point description: | |
| Summary of Kaplan-Meier Estimates for Progression Free Survival at Any Site | |
| End point type | Secondary |
| End point timeframe: | |
| time from baseline to data cutoff (25 Sept 2007); approximately 2 years | |

| End point values | Cohort A | Cohort B | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 143 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.60 (1.87 to 3.25) | 1.87 (1.84 to 2.63) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|---|------------------|
| End point title | Overall survival |
| End point description: | |
| Overall survival (OS) defined as the time from initiation of investigational product to death due to any cause. | |
| End point type | Secondary |
| End point timeframe: | |
| time from baseline to data cutoff (25 Sept 2007); approximately 2 years | |

| End point values | Cohort A | Cohort B | | |
|----------------------------------|-----------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 143 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10.78 (7.95 to 12.68) | 5.82 (4.78 to 7.89) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of site of first progression

| | |
|---|--------------------------------------|
| End point title | Summary of site of first progression |
| End point description: Overall survival (OS) defined as the time from initiation of investigational product to death due to any cause. | |
| End point type | Secondary |
| End point timeframe: time from baseline to data cutoff (25 Sept 2007); approximately 2 years | |

| End point values | Cohort A | Cohort B | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 | 143 | | |
| Units: participants | | | | |
| CNS progression | 69 | 72 | | |
| Non-CNS progression | 1 | 10 | | |
| CNS and Non-CNS progression | 12 | 36 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Primary cause of death

| | |
|---|------------------------|
| End point title | Primary cause of death |
| End point description: Primary causes of death as reported by investigator | |
| End point type | Secondary |
| End point timeframe: time from baseline to data cutoff (25 Sept 2007); approximately 2 years | |

| End point values | Cohort A | Cohort B | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 95 | 147 | | |
| Units: participants | | | | |
| Disease under study | 74 | 124 | | |
| Other | 4 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

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

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | EGF105084/Cohort B |
|-----------------------|--------------------|

Reporting group description:

EGF105084/Cohort B

| | |
|-----------------------|--------------------|
| Reporting group title | EGF105084/Cohort A |
|-----------------------|--------------------|

Reporting group description:

EGF105084/Cohort A

| Serious adverse events | EGF105084/Cohort B | EGF105084/Cohort A | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 52 / 147 (35.37%) | 36 / 95 (37.89%) | |
| number of deaths (all causes) | 48 | 20 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 2 / 147 (1.36%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Complication associated with device | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Performance status decreased | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumothorax | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 147 (2.72%) | 5 / 95 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Depression | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 2 / 95 (2.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood phosphorus increased | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 4 / 147 (2.72%) | 2 / 95 (2.11%) | |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 147 (0.00%) | 2 / 95 (2.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukoencephalopathy | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraplegia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Partial seizures | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 5 / 147 (3.40%) | 3 / 95 (3.16%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 147 (2.72%) | 6 / 95 (6.32%) | |
| occurrences causally related to treatment / all | 3 / 4 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 3 / 147 (2.04%) | 3 / 95 (3.16%) | |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal perforation | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 147 (3.40%) | 3 / 95 (3.16%) | |
| occurrences causally related to treatment / all | 2 / 5 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Exfoliative rash | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Myopathy | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acinetobacter infection | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 3 / 147 (2.04%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis bacterial | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Necrotising fasciitis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 2 / 95 (2.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary tuberculosis | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 147 (2.72%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 4 / 95 (4.21%) | |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 95 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 95 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | EGF105084/Cohort B | EGF105084/Cohort A | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 131 / 147 (89.12%) | 90 / 95 (94.74%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 13 / 147 (8.84%) | 4 / 95 (4.21%) | |
| occurrences (all) | 13 | 4 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 7 / 95 (7.37%) | |
| occurrences (all) | 1 | 9 | |
| Weight decreased | | | |
| subjects affected / exposed | 11 / 147 (7.48%) | 5 / 95 (5.26%) | |
| occurrences (all) | 12 | 6 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 147 (3.40%) | 8 / 95 (8.42%) | |
| occurrences (all) | 5 | 11 | |
| Dysgeusia | | | |
| subjects affected / exposed | 5 / 147 (3.40%) | 5 / 95 (5.26%) | |
| occurrences (all) | 5 | 5 | |
| Headache | | | |
| subjects affected / exposed | 29 / 147 (19.73%) | 23 / 95 (24.21%) | |
| occurrences (all) | 40 | 31 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 147 (4.76%) | 5 / 95 (5.26%) | |
| occurrences (all) | 8 | 6 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 15 / 147 (10.20%) | 9 / 95 (9.47%) | |
| occurrences (all) | 18 | 9 | |
| Fatigue | | | |
| subjects affected / exposed | 29 / 147 (19.73%) | 30 / 95 (31.58%) | |
| occurrences (all) | 33 | 31 | |

| | | | |
|---|--------------------------|-------------------------|--|
| Oedema peripheral subjects affected / exposed occurrences (all) | 16 / 147 (10.88%) 18 | 6 / 95 (6.32%) 6 | |
| Pyrexia subjects affected / exposed occurrences (all) | 6 / 147 (4.08%) 7 | 5 / 95 (5.26%) 6 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 4 / 147 (2.72%) 5 | 5 / 95 (5.26%) 5 | |
| Constipation subjects affected / exposed occurrences (all) | 16 / 147 (10.88%) 19 | 9 / 95 (9.47%) 10 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 92 / 147 (62.59%) 153 | 71 / 95 (74.74%) 113 | |
| Dry mouth subjects affected / exposed occurrences (all) | 6 / 147 (4.08%) 7 | 6 / 95 (6.32%) 7 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 9 / 147 (6.12%) 10 | 3 / 95 (3.16%) 3 | |
| Nausea subjects affected / exposed occurrences (all) | 47 / 147 (31.97%) 58 | 29 / 95 (30.53%) 42 | |
| Vomiting subjects affected / exposed occurrences (all) | 39 / 147 (26.53%) 50 | 24 / 95 (25.26%) 37 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 8 / 147 (5.44%) 9 | 5 / 95 (5.26%) 6 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 11 / 147 (7.48%) 12 | 6 / 95 (6.32%) 8 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-------------------|------------------|--|
| Acne | | | |
| subjects affected / exposed | 11 / 147 (7.48%) | 6 / 95 (6.32%) | |
| occurrences (all) | 12 | 8 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 10 / 147 (6.80%) | 6 / 95 (6.32%) | |
| occurrences (all) | 10 | 8 | |
| Dry skin | | | |
| subjects affected / exposed | 15 / 147 (10.20%) | 7 / 95 (7.37%) | |
| occurrences (all) | 16 | 9 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 21 / 147 (14.29%) | 16 / 95 (16.84%) | |
| occurrences (all) | 27 | 16 | |
| Pruritus | | | |
| subjects affected / exposed | 13 / 147 (8.84%) | 8 / 95 (8.42%) | |
| occurrences (all) | 13 | 9 | |
| Rash | | | |
| subjects affected / exposed | 37 / 147 (25.17%) | 40 / 95 (42.11%) | |
| occurrences (all) | 44 | 48 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 7 / 147 (4.76%) | 5 / 95 (5.26%) | |
| occurrences (all) | 10 | 6 | |
| Back pain | | | |
| subjects affected / exposed | 6 / 147 (4.08%) | 6 / 95 (6.32%) | |
| occurrences (all) | 6 | 6 | |
| Bone pain | | | |
| subjects affected / exposed | 8 / 147 (5.44%) | 2 / 95 (2.11%) | |
| occurrences (all) | 8 | 2 | |
| Pain in extremity | | | |
| subjects affected / exposed | 7 / 147 (4.76%) | 8 / 95 (8.42%) | |
| occurrences (all) | 8 | 9 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 5 / 95 (5.26%) | |
| occurrences (all) | 2 | 6 | |
| Urinary tract infection | | | |

| | | | |
|--|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 8 / 147 (5.44%) 9 | 7 / 95 (7.37%) 8 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 28 / 147 (19.05%) | 16 / 95 (16.84%) | |
| occurrences (all) | 29 | 17 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 11 / 147 (7.48%) | 5 / 95 (5.26%) | |
| occurrences (all) | 14 | 8 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 13 October 2005 | Amendment 01 (13-Oct-2005) - Country specific amendment for Germany and Poland to remove the requirement for specialized radiological assessments using positron emission tomography (PET). |
| 21 December 2005 | Amendment 02 (21-Dec-2005) – Country specific amendment for Japan to (1) add a pharmacokinetic component to the protocol (2) add a Go/No Go decision based on dose limiting toxicities in first 6 Japanese subjects (3) remove option to enroll into an open-label extension phase (lapatinib combination therapy) and (4) elect as an option, on a site basis, the specialized radiological assessments using positron emission tomography (PET) |
| 19 June 2006 | Amendment 03 (19-Jun-2006) – Optional protocol extension added for subjects on monotherapy lapatinib who develop disease progression in the CNS, to receive the combination of lapatinib and capecitabine, protocol clarifications added throughout. |
| 22 January 2007 | Amendment 04 (22-Jan-2007) – Country specific amendment for Japan, to allow the trial to remain open in Japan beyond the full-enrollment closure globally, in order to allow the participation of at least 6 Japanese subjects and the collection of PK and safety data. |
| 29 May 2008 | Amendment 05 (29-May-2008) –Additional safety information and treatment guidelines related to hepatotoxicity added. |
| 29 August 2012 | <p>Amendment 06 (29-Aug-2012)</p> <ul style="list-style-type: none">- Discontinuation of many specific efficacy and safety assessments. The study was stopped for subjects in post treatment follow up. Continued access to study treatment lapatinib was permitted for subject ongoing at the time of implementation of this amendment.- Update to Prohibited Medications was added- Extension phases of the study were removed <p>This amendment was not circulated outside Sponsor (GSK) and later replaced by Protocol Amendment 07 which re-instated the extension phase of the study.</p> |
| 15 April 2013 | <p>Protocol Amendment 07 was implemented to discontinue collection of many study-specific assessments while allowing the one subject receiving treatment to have continued access to the treatment until the occurrence of unacceptable toxicity or disease progression (as determined by the investigator).</p> <p>Amendment 07 (15-Apr-2013), introduced the following changes:</p> <ul style="list-style-type: none">- Re-instated the Extension phase of the study- Continued access to treatment under one of the extension phases permitted.- Reduced the number of study assessments in the extension phases.- Updated information on LAP016A2305/EGF111438 results added to align with Supplement 01 of Lapatinib Investigator's Brochure version 13- Updated safety guidelines<ul style="list-style-type: none">- Addition of the efficacy results of the Study EGF111438 interim analysis (CSR dated 16-Oct-2012) <p>Amendment 08 (03-Oct-2016), introduced the following changes:</p> <ul style="list-style-type: none">- Deleted or replaced references to GSK or its staff with that of Novartis and its authorized agents.- Administrative changes to align with Novartis processes and procedures. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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| 3 objectives not in protocol were initially registered in error. There was no analysis of these outcomes and there should not have been 2 participants were counted twice when they moved from one site to another. 1 in Japan and 1 in US. Actual global |
|---|

Notes: