

**Clinical trial results:****A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 versus Capecitabine in subjects with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes****Summary**

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2005-004009-26 |
| Trial protocol | HU BE CZ LT DE FR IT GR BG ES |
| Global end of trial date | 11 December 2017 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 13 June 2020 |
| First version publication date | 20 February 2019 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set Results were initially posted at primary completion date cut-off. Updated version includes new data added to full data set at study completion date. |

Trial information**Trial identification**

| | |
|-----------------------|----------------|
| Sponsor protocol code | E7389-G000-301 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00337103 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Eisai Inc. |
| Sponsor organisation address | Woodcliff Lake, New Jersey, United States, 07677 |
| Public contact | Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.com |
| Scientific contact | Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.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 | Interim |
| Date of interim/final analysis | 12 March 2012 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 March 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of E7389 versus capecitabine monotherapy, in terms of overall survival (OS) and progression-free survival (PFS) in subjects with locally advanced or metastatic breast cancer.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 20 September 2006 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 3 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 63 |
| Country: Number of subjects enrolled | Belgium: 42 |
| Country: Number of subjects enrolled | Bulgaria: 15 |
| Country: Number of subjects enrolled | Czech Republic: 23 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Greece: 3 |
| Country: Number of subjects enrolled | Hungary: 42 |
| Country: Number of subjects enrolled | Italy: 8 |

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Lithuania: 6 |
| Country: Number of subjects enrolled | Russian Federation: 300 |
| Country: Number of subjects enrolled | Argentina: 67 |
| Country: Number of subjects enrolled | Brazil: 120 |
| Country: Number of subjects enrolled | Mexico: 22 |
| Country: Number of subjects enrolled | Australia: 14 |
| Country: Number of subjects enrolled | Israel: 17 |
| Country: Number of subjects enrolled | Croatia: 9 |
| Country: Number of subjects enrolled | Poland: 41 |
| Country: Number of subjects enrolled | Romania: 34 |
| Country: Number of subjects enrolled | Serbia: 20 |
| Country: Number of subjects enrolled | Ukraine: 122 |
| Country: Number of subjects enrolled | Canada: 25 |
| Country: Number of subjects enrolled | United States: 62 |
| Country: Number of subjects enrolled | Singapore: 6 |
| Country: Number of subjects enrolled | Taiwan: 19 |
| Country: Number of subjects enrolled | South Africa: 12 |
| Worldwide total number of subjects | 1102 |
| EEA total number of subjects | 296 |

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) | 944 |
| From 65 to 84 years | 158 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 210 sites across geographic regions (6 regions: North America, Western Europe, Eastern Europe, Latin America, South Africa and Asia) from 01 Apr 2006 to 12 Mar 2012.

Pre-assignment

Screening details:

A total of 1276 participants were enrolled and screened, of which 174 were screen failures and 1102 were randomized in the study. Of the randomized participants, 1090 participants received the study treatment.

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Eribulin Mesylate 1.4 mg/m ² |

Arm description:

Eribulin mesylate 1.4 milligram per square meter (mg/m²) intravenous (IV) infusion given over 2-5 minutes on Days 1 and 8 every 21 days.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Eribulin Mesylate |
| Investigational medicinal product code | E7389 |
| Other name | Halaven |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravascular use |

Dosage and administration details:

Eribulin mesylate 1.4 mg/m² IV infusion given over 2-5 minutes on Days 1 and 8 every 21 days.

| | |
|------------------|--|
| Arm title | Capecitabine 2.5 g/m ² /Day |
|------------------|--|

Arm description:

Capecitabine : Capecitabine 2.5 gram per square meter (g/m²) per (/) day administered orally twice daily in two equal doses on Days 1 to 14 every 21 days.

| | |
|--|--------------------|
| Arm type | Active comparator |
| 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 2.5 g/m²/day administered orally twice daily in two equal doses on Days 1 to 14 every 21 days.

| Number of subjects in period 1 | Eribulin Mesylate 1.4 mg/m² | Capecitabine 2.5 g/m²/Day |
|---------------------------------------|---|---|
| Started | 554 | 548 |
| Treated (Safety Population) | 544 | 546 |
| Completed | 0 | 0 |
| Not completed | 554 | 548 |
| Physician decision | 15 | 14 |
| Consent withdrawn by subject | 8 | 5 |
| Adverse event, non-fatal | 45 | 59 |
| Subject Choice | 34 | 27 |
| Death | 1 | - |
| Progressive Disease | 414 | 410 |
| Not specified | 5 | 6 |
| Lost to follow-up | 1 | 2 |
| Clinical Progression | 27 | 24 |
| Entry Criteria Not Met | 4 | 1 |

Baseline characteristics

Reporting groups

| | |
|---|---|
| Reporting group title | Eribulin Mesylate 1.4 mg/m ² |
| Reporting group description: Eribulin mesylate 1.4 milligram per square meter (mg/m ²) intravenous (IV) infusion given over 2-5 minutes on Days 1 and 8 every 21 days. | |
| Reporting group title | Capecitabine 2.5 g/m ² /Day |
| Reporting group description: Capecitabine : Capecitabine 2.5 gram per square meter (g/m ²) per (/) day administered orally twice daily in two equal doses on Days 1 to 14 every 21 days. | |

| Reporting group values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | Total |
|------------------------------------|---|--|-------|
| Number of subjects | 554 | 548 | 1102 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----------------|-----------------|------|
| Age continuous Units: years arithmetic mean standard deviation | 53.8 ± 10.37 | 52.8 ± 10.20 | - |
| Gender categorical Units: Subjects | | | |
| Female | 554 | 548 | 1102 |
| Male | 0 | 0 | 0 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 18 | 18 | 36 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 15 | 16 | 31 |
| White | 496 | 495 | 991 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 25 | 19 | 44 |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Eribulin Mesylate 1.4 mg/m ² |
| Reporting group description: Eribulin mesylate 1.4 milligram per square meter (mg/m ²) intravenous (IV) infusion given over 2-5 minutes on Days 1 and 8 every 21 days. | |
| Reporting group title | Capecitabine 2.5 g/m ² /Day |
| Reporting group description: Capecitabine : Capecitabine 2.5 gram per square meter (g/m ²) per (/) day administered orally twice daily in two equal doses on Days 1 to 14 every 21 days. | |

Primary: Overall Survival (OS)

| | |
|--|--------------------------------------|
| End point title | Overall Survival (OS) ^[1] |
| End point description: OS was measured from the date of randomization until the date of death from any cause, or the last date the subject was known to be alive. Subjects who were lost to follow-up or who were alive at the date of data cutoff were censored. The censoring rules for OS were as follows: 1) if the subject was still alive at data cutoff, the date of data cutoff was considered the end date, and 2) if the subject was lost to follow-up before data cutoff, the date they were last known to be alive was considered the end date. Subjects who survived past the end of the study were counted as in the full study period. If death occurred after data cutoff, the end date was to be censored at the time of data cutoff. Data was analyzed using the Intent-to-Treat (ITT) Population defined as all subject who were randomized. | |
| End point type | Primary |
| End point timeframe: From date of randomization until date of death from any cause, assessed up to data cutoff date of 12 Mar 2012, or up to approximately 6 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: Only descriptive data was planned to be analysed for this endpoint. | |

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 554 | 548 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 484 (462 to 536) | 440 (400 to 487) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival (PFS)

| | |
|--|--|
| End point title | Progression Free Survival (PFS) ^[2] |
| End point description: PFS was defined as the time (in days) from the date of randomization to the date of the first sign of disease progression based on Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (v 1.1) | |

or date of death, regardless of cause. Disease progression was measured by computed tomography (CT) and magnetic resonance imaging (MRI) performed on lesions targeted at baseline for tumor assessment. Disease progression (as assessed by independent review of the imaging scans) per RECIST v 1.1 was defined as at least a 20% increase in the sum of the diameters of the target lesions (taking as reference the smallest sum on study, including the baseline sum if that is the smallest), and an absolute increase of at least 5 millimeter (mm). Note that the appearance of one or more new lesions was also considered as disease progression. Data was analyzed using the ITT Population defined as all subject who were randomized.

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

End point timeframe:

From date of randomization to the date of disease progression or death (whichever occurred first), assessed up to data cutoff date of 12 Mar 2012 or up to approximately 6 years

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: Only descriptive data was planned to be analysed for this endpoint.

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 554 | 548 | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 126 (106 to 131) | 129 (120 to 147) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Global Health Status/Quality of Life (QoL) Measured by European Organization for the Treatment of Cancer Quality of Life Core Questionnaire Scores Based on Core 30 Items (EORTC-QLQ-C30) at Week 6

| | |
|-----------------|---|
| End point title | Change From Baseline in Global Health Status/Quality of Life (QoL) Measured by European Organization for the Treatment of Cancer Quality of Life Core Questionnaire Scores Based on Core 30 Items (EORTC-QLQ-C30) at Week 6 |
|-----------------|---|

End point description:

EORTCQLQ-C30: cancer-specific instrument with 30 questions to assess the subject QoL. First 28 questions used to evaluate 5 functional scales (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, nausea and vomiting, pain) and single items (dyspnea, appetite loss, insomnia, constipation, diarrhea, financial difficulties). Each of these 28 questions assessed on 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much); functional scales: higher score=better level of functioning; symptom scale: higher score=more severe symptoms; for single items: higher score=more severe problem. Last 2 questions used to evaluate global health status (GHS)/QoL. Each question was assessed on 7-point scale (1=very poor to 7=excellent). Scores averaged, transformed to 0-100 scale; higher score=better quality of life/better level of functioning. ITT Population: subjects who were randomized. Here, overall number of subjects analyzed are those who were evaluable for this outcome measure.

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

End point timeframe:

Baseline and Week 6

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 438 | 406 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 0.1 (± 19.23) | 1.7 (± 20.69) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for the Treatment of Cancer Quality of Life Core Questionnaire Scores Based on Breast Cancer Specific 23 Items (EORTC-QLQ- BR 23) at Week 6

| | |
|-----------------|---|
| End point title | Change From Baseline in European Organization for the Treatment of Cancer Quality of Life Core Questionnaire Scores Based on Breast Cancer Specific 23 Items (EORTC-QLQ- BR 23) at Week 6 |
|-----------------|---|

End point description:

EORTC-QLQ-BR23:disease-specific module for breast cancer developed as a supplement for the EORTC-QLQ-C30 to assess quality of life of participants with breast cancer. The scores from 23 items of QLQ-BR23 included functional scales (body image, sexual functioning, sexual enjoyment, future perspective), symptom scales (systemic therapy side effects, breast symptoms, arm symptoms, upset by hair loss). Each item was rated on a scale of 1 to 4 to record level of intensity (1= not at all, 2= a little, 3= quite a bit, 4= very much) within each scales. Scores averaged and transformed to 0-100 scale. High score indicated high/better level of functioning/healthy functioning. Negative change from Baseline indicated deterioration in QOL and positive change from Baseline indicated an improvement in QOL. ITT Population: all subjects who were randomized. Here, "number analyzed" signifies the subjects who were evaluable for this outcome measure for individual row.

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

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|---|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 554 | 548 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Body Image: (n=441, 411) | 0.7 (± 21.26) | 4.8 (± 21.80) | | |
| Sexual functioning: (n=418, 381) | 1.2 (± 14.75) | -0.1 (± 16.62) | | |
| Sexual enjoyment: (n=82, 96) | 0.8 (± 21.58) | 3.1 (± 17.49) | | |
| Future perspective: (n=439, 410) | 7.7 (± 28.48) | 10.0 (± 30.84) | | |
| Systemic therapy side effects: (n=440, 415) | 4.5 (± 15.55) | -1.2 (± 14.73) | | |
| Breast Symptoms: (n=434, 407) | -3.4 (± 16.55) | -3.6 (± 16.20) | | |
| Arm Symptoms: (n=437, 411) | -4.2 (± 17.94) | -3.4 (± 18.65) | | |
| Upset by hair loss: (n=91, 56) | -4.4 (± 32.66) | -10.1 (± 29.76) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR): Independent Review

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|-----------------|---|
| End point title | Objective Response Rate (ORR): Independent Review |
|-----------------|---|

End point description:

ORR was defined as the percentage of subjects with a best overall response of complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v 1.1). CR is defined as disappearance of all target lesions and non-target lesions. All pathological lymph nodes (whether target and non-target), must have reduction in their short axis to less than 10 mm. PR is defined as at least 30% decrease in the sum of the long diameter LD (hereafter referred to as sum of LD) of all target lesions, as compared with Baseline summed LD.

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

End point timeframe:

From date of randomization until date of first documentation of CR or PR, assessed up to data cutoff date of 12 Mar 2012 or up to approximately 6 years

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 554 | 548 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 90%) | 11.0 (8.5 to 13.9) | 11.5 (8.9 to 14.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR): Independent Review

| | |
|-----------------|--|
| End point title | Duration of Response (DOR): Independent Review |
|-----------------|--|

End point description:

DOR was defined as the time from first documented CR or PR until disease progression or death from any cause for those subjects with a confirmed PR or CR measured by RECIST v1.1. CR defined as disappearance of all target and non-target lesions. All pathological lymph nodes (whether target and non-target), must have reduction in their short axis to less than 10 mm. PR defined as at least 30% decrease in the sum of the long diameter LD (hereafter referred to as sum of LD) of all target lesions, as compared with Baseline summed LD. Data was analyzed using for a subset of subjects in the ITT Population who had a response. Here, "overall number of subjects analyzed" are the subjects who were evaluable for this outcome measure.

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

End point timeframe:

From first documented CR or PR until date of recurrent or progressive disease or death, assessed up to data cutoff date of 12 Mar 2012 or up to approximately 6 years

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 | 63 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 198 (150 to 273) | 330 (208 to 541) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate

| | |
|-----------------|-----------------------|
| End point title | Overall Survival Rate |
|-----------------|-----------------------|

End point description:

One-, two-, and three- year's survival rates were defined as the percentage of subjects who were alive at one, two, and three years respectively, and estimated using the Kaplan–Meier method and Greenwood Formula. ITT population included all subjects who were randomized.

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

End point timeframe:

From the date of randomization to Year 1, 2 and 3

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 554 | 548 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| At 1-year | 0.644 (0.604 to 0.684) | 0.580 (0.538 to 0.622) | | |
| At 2-years | 0.328 (0.289 to 0.368) | 0.298 (0.259 to 0.337) | | |
| At 3-years | 0.178 (0.144 to 0.212) | 0.145 (0.113 to 0.177) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pain Intensity by Visual Analog Scale (VAS) until 30 Days after the Last Dose of Study Drug

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|-----------------|---|
| End point title | Change From Baseline in Pain Intensity by Visual Analog Scale (VAS) until 30 Days after the Last Dose of Study Drug |
|-----------------|---|

End point description:

Pain intensity was measured by marking a single vertical line that crosses a 1-100 mm unmarked VAS scale. The left-end of the visual analog scale was labelled "least possible pain" and the right-end of the visual analog scale was labelled "worst possible pain". The pain rating ranged from 0 to 100, with a higher score indicating more pain. A negative change score indicated improvement. ITT Population included all subjects who were randomized. Here, "overall number of subjects analyzed" are the subjects who were evaluable for the outcome measure.

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

End point timeframe:

First dose of study drug (Baseline) up to 30 days after last dose of study drug (up to approximately 6 years 3 months)

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 431 | 431 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -3.7 (± 22.80) | 0.4 (± 22.90) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Consumption of Analgesics During the Study

| | |
|-----------------|--|
| End point title | Number of Subjects With Consumption of Analgesics During the Study |
|-----------------|--|

End point description:

Subjects took analgesics as concomitant pain medications which are defined as pain medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on/after the day of the first dose of study drug up to 30 days after the last dose of study drug medication. Safety population included all subjects who received at least one dose of study treatment.

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

End point timeframe:

First dose of study drug (Baseline) up to 30 days after last dose of study drug (up to approximately 6 years 3 months)

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 544 | 546 | | |
| Units: subjects | 222 | 196 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

Safety population defined as all subjects who received at least one dose of study treatment. TEAEs included both SAEs as well as non-SAEs.

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

End point timeframe:

First dose of study drug (Baseline) up to 30 days after last dose of study drug (up to approximately 6 years 3 months)

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 544 | 546 | | |
| Units: subjects | | | | |
| TEAEs | 512 | 494 | | |
| SAEs | 95 | 115 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Markedly Abnormal Parameter Values

| | |
|-----------------|---|
| End point title | Number of Subjects With Treatment-emergent Markedly Abnormal Parameter Values |
|-----------------|---|

End point description:

Safety population defined as all subjects who received at least one dose of study treatment.

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

End point timeframe:

First dose of study drug (Baseline) up to 30 days after last dose of study drug (up to approximately 6 years 3 months)

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 544 | 546 | | |
| Units: subjects | 362 | 224 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Took at Least One Concomitant Medication

| | |
|-----------------|---|
| End point title | Number of Subjects Who Took at Least One Concomitant Medication |
|-----------------|---|

End point description:

Concomitant medications included medications that either (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the first dose of study drug up to 30 days after the last dose of study drug. Safety population included all subjects who received at least one dose of study treatment.

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

End point timeframe:

First dose of study drug (Baseline) up to 30 days after last dose of study drug (up to approximately 6 years 3 months)

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|-----------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 544 | 546 | | |
| Units: subjects | 496 | 483 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Eribulin mesylate Exposure

| | |
|-----------------|--|
| End point title | Duration of Eribulin mesylate Exposure |
|-----------------|--|

End point description:

Data have been reported per primary analysis completion stage and final analysis completion stage. After primary analysis completion (at cutoff date of 12 March 2012), only 10 subjects were still receiving study treatment.

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

End point timeframe:

Up to approximately 6 years for primary analysis completion stage, Up to approximately 6 years 2 months for final analysis completion stage

| End point values | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 554 | 548 | | |
| Units: days | | | | |
| median (full range (min-max)) | | | | |
| At primary analysis completion stage (n= 544, 546) | 125.0 (21 to 1372) | 119.0 (21 to 1442) | | |
| At final analysis completion stage (n=5, 5) | 1743.0 (1561 to 2219) | 1506.0 (1175 to 2296) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Eribulin mesylate

| | |
|--|---|
| End point title | Plasma Concentrations of Eribulin mesylate ^[3] |
| End point description: Pharmacokinetic (PK) analysis set included all subjects who have received at least one dose of E7389 and have at least one quantifiable E7389 concentration. Here, "number analyzed" signifies the subjects who were evaluable for this outcome measure for given time points. | |
| End point type | Secondary |
| End point timeframe: Cycle 1 Day 1: 5-10 minutes(min), 15-30 min, 30-60 min, 60-90 min, 2-4 hours(hrs), 4-8 hrs, 10-24 hrs, 48-72 hrs, 72-96 hrs, 96-120 hrs after the start of infusion of Eribulin mesylate (Duration of each cycle is 21 days) | |
| Notes: [3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive data was planned to be analysed for this endpoint. | |

| End point values | Eribulin Mesylate 1.4 mg/m ² | | | |
|--|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 173 | | | |
| Units: nanogram per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| 5-10 minutes (n=172) | 415.8 (± 719.5) | | | |
| 15-30 minutes (n=57) | 152.6 (± 70.51) | | | |
| 30-60 minutes (n=58) | 95.5 (± 87.90) | | | |
| 60-90 minutes (n=58) | 52.7 (± 79.33) | | | |
| 2-4 hours (n=85) | 20.7 (± 32.81) | | | |
| 4-8 hours (n=78) | 10.0 (± 5.40) | | | |

| | | | | |
|---------------------|---------------|--|--|--|
| 10-24 hours (n=44) | 5.8 (± 3.72) | | | |
| 48-72 hours (n=40) | 3.7 (± 2.58) | | | |
| 72-96 hours (n=37) | 2.4 (± 1.60) | | | |
| 96-120 hours (n=41) | 7.6 (± 38.75) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug (Baseline) up to 30 days after last dose of study drug (up to approximately 6 years 3 months)

Adverse event reporting additional description:

Data was analyzed using Safety Population defined as all subjects who received at least one dose of study treatment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Eribulin Mesylate 1.4 mg/m ² |
|-----------------------|---|

Reporting group description:

Eribulin mesylate 1.4 mg/m² IV infusion given over 2-5 minutes on Days 1 and 8 every 21 days.

| | |
|-----------------------|--|
| Reporting group title | Capecitabine 2.5 g/m ² /Day |
|-----------------------|--|

Reporting group description:

Capecitabine : Capecitabine 2.5 g/m²/day administered orally twice daily in two equal doses on Days 1 to 14 every 21 days.

| Serious adverse events | Eribulin Mesylate 1.4 mg/m ² | Capecitabine 2.5 g/m ² /Day | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 95 / 544 (17.46%) | 115 / 546 (21.06%) | |
| number of deaths (all causes) | 442 | 459 | |
| number of deaths resulting from adverse events | 26 | 36 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant Ascites | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant Pleural Effusion | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to Central Nervous System | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to Liver | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Metastases to Meninges | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to Ovary | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to Peritoneum | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to Pleura | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm Malignant | | | |
| subjects affected / exposed | 7 / 544 (1.29%) | 4 / 546 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 6 | 0 / 4 | |
| Oncologic Complication | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Rectal Cancer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour Pain | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep Vein Thrombosis | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 3 / 546 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Malignant Breast Lump Removal | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 544 (0.55%) | 4 / 546 (0.73%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 2 | |
| Extravasation | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 544 (0.55%) | 4 / 546 (0.73%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General Physical Health Deterioration | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 3 / 546 (0.55%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Generalized Oedema | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Influenza Like Illness | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injection Site Extravasation | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal Inflammation | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-Organ Failure | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 544 (0.55%) | 5 / 546 (0.92%) | |
| occurrences causally related to treatment / all | 1 / 3 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden Death | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast | | | |

| | | | |
|---|------------------|------------------|--|
| disorders | | | |
| Vaginal Haemorrhage | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute Respiratory Failure | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 13 / 544 (2.39%) | 17 / 546 (3.11%) | |
| occurrences causally related to treatment / all | 4 / 20 | 2 / 22 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrothorax | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural Effusion | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| 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 | 1 / 544 (0.18%) | 3 / 546 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory Distress | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory Failure | | | |
| subjects affected / exposed | 5 / 544 (0.92%) | 7 / 546 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 5 | |
| Tracheal Stenosis | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wheezing | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |

| | | | |
|---|-----------------|-----------------|--|
| Aspartate Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemoglobin Decreased | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic Enzyme Increased | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Troponin Increased | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental Overdose | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral Neck Fracture | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur Fracture | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip Fracture | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Humerus Fracture | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint Dislocation | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar Vertebral Fracture | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina Pectoris | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Failure | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac Tamponade | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory Arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiogenic Shock | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Cardiopulmonary Failure | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Left Ventricular Dysfunction | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial Infarction | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial Effusion | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebellar Infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebrovascular Accident | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Coma Hepatic | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Convulsion | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Depressed Level of Consciousness | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial Paresis | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 544 (0.37%) | 4 / 546 (0.73%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial Pressure Increased | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Lethargy | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myoclonic Epilepsy | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (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 | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral Motor Neuropathy | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral Sensory Neuropathy | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Simple Partial Seizures | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Cord Compression | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient Ischaemic Attack | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 544 (0.55%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile Neutropenia | | | |
| subjects affected / exposed | 7 / 544 (1.29%) | 4 / 546 (0.73%) | |
| occurrences causally related to treatment / all | 7 / 8 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 4 / 544 (0.74%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 10 / 544 (1.84%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 10 / 10 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 15 / 546 (2.75%) | |
| occurrences causally related to treatment / all | 1 / 1 | 14 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 7 / 546 (1.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 8 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 9 / 546 (1.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 6 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic Failure | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatitis Toxic | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Palmar-Plantar Erythrodysaesthesia Syndrome | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Failure | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Renal Failure Acute | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back Pain | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone Pain | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular Weakness | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological Fracture | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (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 | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 3 / 546 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Hepatitis C | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (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 | 1 / 544 (0.18%) | 0 / 546 (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 | 4 / 544 (0.74%) | 4 / 546 (0.73%) | |
| occurrences causally related to treatment / all | 1 / 4 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pneumonia Klebsiella | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory Tract Infection | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 544 (0.37%) | 4 / 546 (0.73%) | |
| occurrences causally related to treatment / all | 2 / 4 | 4 / 5 | |
| deaths causally related to treatment / all | 1 / 2 | 1 / 1 | |
| Soft Tissue Infection | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal Infection | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous Abscess | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 0 / 546 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 9 / 546 (1.65%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte Imbalance | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 544 (0.18%) | 2 / 546 (0.37%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatremia | | | |
| subjects affected / exposed | 0 / 544 (0.00%) | 1 / 546 (0.18%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Eribulin Mesylate 1.4 mg/m² | Capecitabine 2.5 g/m²/Day | |
|---|---|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 509 / 544 (93.57%) | 489 / 546 (89.56%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 47 / 544 (8.64%) | 23 / 546 (4.21%) | |
| occurrences (all) | 103 | 41 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 43 / 544 (7.90%) | 27 / 546 (4.95%) | |
| occurrences (all) | 113 | 49 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 29 / 544 (5.33%) | 22 / 546 (4.03%) | |
| occurrences (all) | 38 | 43 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 30 / 544 (5.51%) | 29 / 546 (5.31%) | |
| occurrences (all) | 38 | 31 | |
| Headache | | | |
| subjects affected / exposed | 67 / 544 (12.32%) | 55 / 546 (10.07%) | |
| occurrences (all) | 133 | 94 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 73 / 544 (13.42%) | 38 / 546 (6.96%) | |
| occurrences (all) | 131 | 47 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|--------------------|-------------------|--|
| Anaemia | | | |
| subjects affected / exposed | 102 / 544 (18.75%) | 96 / 546 (17.58%) | |
| occurrences (all) | 237 | 194 | |
| Leukopenia | | | |
| subjects affected / exposed | 171 / 544 (31.43%) | 57 / 546 (10.44%) | |
| occurrences (all) | 537 | 170 | |
| Neutropenia | | | |
| subjects affected / exposed | 292 / 544 (53.68%) | 87 / 546 (15.93%) | |
| occurrences (all) | 914 | 211 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 27 / 544 (4.96%) | 29 / 546 (5.31%) | |
| occurrences (all) | 48 | 42 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 83 / 544 (15.26%) | 79 / 546 (14.47%) | |
| occurrences (all) | 165 | 113 | |
| Fatigue | | | |
| subjects affected / exposed | 91 / 544 (16.73%) | 82 / 546 (15.02%) | |
| occurrences (all) | 193 | 116 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 26 / 544 (4.78%) | 35 / 546 (6.41%) | |
| occurrences (all) | 37 | 60 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 35 / 544 (6.43%) | 36 / 546 (6.59%) | |
| occurrences (all) | 42 | 41 | |
| Pyrexia | | | |
| subjects affected / exposed | 67 / 544 (12.32%) | 27 / 546 (4.95%) | |
| occurrences (all) | 124 | 33 | |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 32 / 544 (5.88%) | 46 / 546 (8.42%) | |
| occurrences (all) | 51 | 68 | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 31 / 544 (5.70%) | 39 / 546 (7.14%) | |
| occurrences (all) | 38 | 52 | |
| Constipation | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 42 / 544 (7.72%) 70 | 46 / 546 (8.42%) 58 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 77 / 544 (14.15%) 124 | 154 / 546 (28.21%) 363 | |
| Nausea subjects affected / exposed occurrences (all) | 121 / 544 (22.24%) 259 | 131 / 546 (23.99%) 226 | |
| Stomatitis subjects affected / exposed occurrences (all) | 27 / 544 (4.96%) 38 | 31 / 546 (5.68%) 42 | |
| Vomiting subjects affected / exposed occurrences (all) | 63 / 544 (11.58%) 87 | 89 / 546 (16.30%) 141 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 45 / 544 (8.27%) 56 | 44 / 546 (8.06%) 61 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 49 / 544 (9.01%) 62 | 51 / 546 (9.34%) 77 | |
| Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all) | 9 / 544 (1.65%) 12 | 38 / 546 (6.96%) 82 | |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 188 / 544 (34.56%) 263 | 22 / 546 (4.03%) 24 | |
| Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all) | 1 / 544 (0.18%) 1 | 244 / 546 (44.69%) 735 | |
| Musculoskeletal and connective tissue disorders Arthralgia | | | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 42 / 544 (7.72%) | 31 / 546 (5.68%) | |
| occurrences (all) | 76 | 53 | |
| Back pain | | | |
| subjects affected / exposed | 55 / 544 (10.11%) | 43 / 546 (7.88%) | |
| occurrences (all) | 86 | 75 | |
| Bone pain | | | |
| subjects affected / exposed | 50 / 544 (9.19%) | 42 / 546 (7.69%) | |
| occurrences (all) | 94 | 75 | |
| Myalgia | | | |
| subjects affected / exposed | 30 / 544 (5.51%) | 8 / 546 (1.47%) | |
| occurrences (all) | 38 | 9 | |
| Pain in extremity | | | |
| subjects affected / exposed | 47 / 544 (8.64%) | 37 / 546 (6.78%) | |
| occurrences (all) | 91 | 68 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 29 / 544 (5.33%) | 26 / 546 (4.76%) | |
| occurrences (all) | 35 | 32 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 68 / 544 (12.50%) | 80 / 546 (14.65%) | |
| occurrences (all) | 91 | 120 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 14 December 2005 | Amendment 01: The protocol was amended to update PFS from secondary objective to primary objective, pharmacogenomic analysis was deleted and Eastern Cooperative Oncology Group (ECOG) performance status was removed from symptom assessments and included as a separate assessment. |
| 02 March 2006 | Amendment 02: The protocol was amended to update number of subjects included in the PK analysis to include a minimum of 200 subjects, requirement for previous exposure to trastuzumab was modified to allow subjects to participate in the study without previous exposure to trastuzumab, confirmation of the frequency of additional bone scans, stability data for E7389, addition of more comprehensive information regarding bone marrow exposure in relation to exclusion criterion #4 and provisions under which the use of bisphosphonates was permitted during the study. |
| 11 May 2006 | Amendment 03: Storage conditions for E7389 were updated according to new stability data. |
| 05 December 2006 | Amendment 04: The protocol was amended to include all subjects, not just those subjects who had measurable lesions for imaging review process by independent review, eligibility criteria were changed to include a more complete representation of the breast cancer population, level of renal function was changed for greater than (>) 50 milliliter/minute creatinine clearance in order to administer the full 2.5 g/m ² starting dose of capecitabine, washout period was added for prior experimental treatments, removed restriction on subjects with prior high dose chemotherapy, added requirement for confirmation of stable brain metastases by scan at screening to ensure scan is available for independent review and allowed for continuation of treatment with E7389 for as long as subjects continue to experience clinical benefit. |
| 31 October 2007 | Amendment 05: The protocol was amendment to update The number of sites participating in the study was increased from 180 to 210. Storage conditions for E7389 were updated to reflect new stability data. |
| 06 March 2008 | Amendment 06: The protocol was amended to update title of the study to remove the requirement for subject's tumors to be refractory to the most recent chemotherapy, eligibility for enrollment into the study was widened to comply with current medical practices in the use of capecitabine, allowed inclusion of subjects with ECOG performance status of up to 2 and complete response (CR) or partial response (PR) was to be assessed a minimum of 5 weeks after start of treatment with a subsequent PD without a confirmation of PR or CR at least 4 weeks later by follow-up scans, allowed investigator more discretion for dose reductions of capecitabine on the first instance of Grade 2 toxicity and specified requirements for bone lesion assessment to note the use of x-ray to confirm whether or not lesions are malignant. Complete response or PR was to be assessed a minimum of 5 weeks after start of treatment with a subsequent PD without a confirmation of PR or CR at least 4 weeks later by follow-up scans but having a subsequent PD assessment was considered SD for the best response. However, CR or PR assessed less than 5 weeks of start of treatment with a subsequent PD was considered PD for the best response. |
| 03 March 2009 | Amendment 07: The protocol was amended to update study timeline to change the date of the end of the study from 31 Mar 2010 to Apr 2012. |

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| 15 September 2014 | Amendment 08: The protocol was amended to update that no further collection of survival follow-up data, quality of life data, pain intensity data, and images by the independent imaging vendor was deemed necessary for the study. |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported