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	• 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 subjetcs 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/m^2) 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/m^2 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/m^2) 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/m^2/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/m^2	Capecitabine 2.5 g/m^2/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	53.8	52.8	
standard deviation	± 10.37	± 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(dysponea, 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

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 legions 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

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/m^2 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/m^2/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/m^2	Capecitabine 2.5 g/m^2/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	42 / 544 (7.72%)	46 / 546 (8.42%)	
occurrences (all)	70	58	
Diarrhoea			
subjects affected / exposed	77 / 544 (14.15%)	154 / 546 (28.21%)	
occurrences (all)	124	363	
Nausea			
subjects affected / exposed	121 / 544 (22.24%)	131 / 546 (23.99%)	
occurrences (all)	259	226	
Stomatitis			
subjects affected / exposed	27 / 544 (4.96%)	31 / 546 (5.68%)	
occurrences (all)	38	42	
Vomiting			
subjects affected / exposed	63 / 544 (11.58%)	89 / 546 (16.30%)	
occurrences (all)	87	141	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	45 / 544 (8.27%)	44 / 546 (8.06%)	
occurrences (all)	56	61	
Dyspnoea			
subjects affected / exposed	49 / 544 (9.01%)	51 / 546 (9.34%)	
occurrences (all)	62	77	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	9 / 544 (1.65%)	38 / 546 (6.96%)	
occurrences (all)	12	82	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	188 / 544 (34.56%)	22 / 546 (4.03%)	
occurrences (all)	263	24	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 544 (0.18%)	244 / 546 (44.69%)	
occurrences (all)	1	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/m2 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.

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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported