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	v1
This version publication date	20 February 2019
First version publication date	20 February 2019

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_medinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., +1 888-274-2378, esi_medinfo@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:

At the date of data cutoff (12 Mar 2012), 10 subjects (5 subjects each in the eribulin mesylate and the capecitabine groups) were still on 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	Experimental
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
Completed	5	5
Not completed	549	543
Physician decision	15	14
Consent withdrawn by subject	8	5
Adverse event, non-fatal	45	59
Subject Choice	34	27
Death	1	-
Progressive Disease	409	405
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 died during the study, the date of death was considered the end date, 2) if the subject was still alive at data cutoff, the date of data cutoff was considered the end date, and 3) 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 Population defined as all participants 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 (full range (min-max))	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 mm. Note that the appearance of one or more new lesions was also considered as PD. Data was analyzed using safety population defined as all subjects who received at least one dose of study treatment.

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 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 (full range (min-max))	126 (106 to 131)	129 (120 to 147)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For each subject, from the first subject first dose till 30 days after the last dose or the cut-off date of 12 March 2012 or up to approximately 6 years

Adverse event reporting additional description:

Treatment emergent adverse events are presented in this section. Data was analyzed using Safety Population defined as all subjects who received at least one dose of study treatment and had a postbaseline safety assessment.

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 / 554 (17.15%)	115 / 546 (21.06%)	
number of deaths (all causes)	442	458	
number of deaths resulting from adverse events	26	36	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant Ascites			
subjects affected / exposed	0 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (1.26%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 6	0 / 2	
Oncologic Complication			
subjects affected / exposed	0 / 554 (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 / 554 (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	
Tumor Pain			
subjects affected / exposed	0 / 554 (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 / 554 (0.36%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensi			
subjects affected / exposed	0 / 554 (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 / 554 (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 Hemorrhagic			
subjects affected / exposed	0 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (0.54%)	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	1 / 554 (0.18%)	4 / 546 (0.73%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 4	
Extravasation			
subjects affected / exposed	1 / 554 (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 / 554 (0.54%)	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	1 / 554 (0.18%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Generalized Oedema			
subjects affected / exposed	0 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (0.54%)	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 / 554 (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 / 554 (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 Hemorrhage			
subjects affected / exposed	0 / 554 (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 / 554 (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 / 554 (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 / 554 (2.35%)	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 / 554 (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 / 554 (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 / 554 (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 / 554 (0.36%)	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 / 554 (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 / 554 (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 / 554 (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 / 554 (0.90%)	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 / 554 (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 / 554 (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 / 554 (0.36%)	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 / 554 (0.36%)	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 / 554 (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 / 554 (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 / 554 (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 / 554 (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	
Electrolyte Imbalance			
subjects affected / exposed	0 / 554 (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	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	1 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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	
Congenital, familial and genetic disorders			
Pericardial Effusion			
subjects affected / exposed	1 / 554 (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	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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	
Tachycardia			
subjects affected / exposed	1 / 554 (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 / 554 (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 / 554 (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 / 554 (0.36%)	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 / 554 (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 / 554 (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 / 554 (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 / 554 (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	
Dysguesia			
subjects affected / exposed	0 / 554 (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 / 554 (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 / 554 (0.36%)	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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (0.36%)	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 / 554 (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 / 554 (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 / 554 (0.54%)	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 / 554 (1.26%)	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 / 554 (0.72%)	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 / 554 (1.81%)	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 / 554 (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 / 554 (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 / 554 (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 / 554 (0.36%)	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 / 554 (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 / 554 (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 / 554 (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 Hemorrhage			
subjects affected / exposed	1 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (0.36%)	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 / 554 (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 / 554 (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 / 554 (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	2 / 554 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	0 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (0.36%)	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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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	
Cellulitis			
subjects affected / exposed	0 / 554 (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 / 554 (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 / 554 (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 / 554 (0.72%)	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 / 554 (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 / 554 (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 / 554 (0.36%)	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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (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	
Hypercalcaemia			
subjects affected / exposed	1 / 554 (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 / 554 (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 / 554 (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 / 554 (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 / 554 (91.88%)	489 / 546 (89.56%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	46 / 554 (8.30%)	23 / 546 (4.21%)	
occurrences (all)	102	41	
Aspartate aminotransferase increased			
subjects affected / exposed	43 / 554 (7.76%)	27 / 546 (4.95%)	
occurrences (all)	112	49	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	29 / 554 (5.23%)	22 / 546 (4.03%)	
occurrences (all)	40	43	
Nervous system disorders			
Dizziness			
subjects affected / exposed	30 / 554 (5.42%)	29 / 546 (5.31%)	
occurrences (all)	38	31	
Headache			
subjects affected / exposed	67 / 554 (12.09%)	55 / 546 (10.07%)	
occurrences (all)	133	94	
Peripheral sensory neuropathy			
subjects affected / exposed	72 / 554 (13.00%)	38 / 546 (6.96%)	
occurrences (all)	126	47	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	102 / 554 (18.41%)	96 / 546 (17.58%)	
occurrences (all)	235	194	
Leukopenia			
subjects affected / exposed	171 / 554 (30.87%)	57 / 546 (10.44%)	
occurrences (all)	513	170	
Neutropenia			

subjects affected / exposed	292 / 554 (52.71%)	87 / 546 (15.93%)	
occurrences (all)	909	212	
Thrombocytopenia			
subjects affected / exposed	27 / 554 (4.87%)	29 / 546 (5.31%)	
occurrences (all)	48	42	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	83 / 554 (14.98%)	78 / 546 (14.29%)	
occurrences (all)	165	112	
Fatigue			
subjects affected / exposed	90 / 554 (16.25%)	82 / 546 (15.02%)	
occurrences (all)	192	116	
Mucosal inflammation			
subjects affected / exposed	26 / 554 (4.69%)	35 / 546 (6.41%)	
occurrences (all)	37	60	
Oedema peripheral			
subjects affected / exposed	35 / 554 (6.32%)	36 / 546 (6.59%)	
occurrences (all)	41	41	
Pyrexia			
subjects affected / exposed	67 / 554 (12.09%)	27 / 546 (4.95%)	
occurrences (all)	124	33	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	32 / 554 (5.78%)	46 / 546 (8.42%)	
occurrences (all)	51	68	
Abdominal Pain Upper			
subjects affected / exposed	31 / 554 (5.60%)	39 / 546 (7.14%)	
occurrences (all)	38	52	
Constipation			
subjects affected / exposed	42 / 554 (7.58%)	46 / 546 (8.42%)	
occurrences (all)	70	58	
Diarrhoea			
subjects affected / exposed	77 / 554 (13.90%)	154 / 546 (28.21%)	
occurrences (all)	122	363	
Nausea			

subjects affected / exposed	121 / 554 (21.84%)	131 / 546 (23.99%)	
occurrences (all)	258	226	
Stomatitis			
subjects affected / exposed	27 / 554 (4.87%)	31 / 546 (5.68%)	
occurrences (all)	38	42	
Vomiting			
subjects affected / exposed	63 / 554 (11.37%)	89 / 546 (16.30%)	
occurrences (all)	87	141	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	45 / 554 (8.12%)	44 / 546 (8.06%)	
occurrences (all)	56	61	
Dyspnoea			
subjects affected / exposed	49 / 554 (8.84%)	51 / 546 (9.34%)	
occurrences (all)	62	77	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	188 / 554 (33.94%)	22 / 546 (4.03%)	
occurrences (all)	265	23	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	42 / 554 (7.58%)	31 / 546 (5.68%)	
occurrences (all)	76	53	
Back pain			
subjects affected / exposed	55 / 554 (9.93%)	43 / 546 (7.88%)	
occurrences (all)	86	76	
Bone pain			
subjects affected / exposed	50 / 554 (9.03%)	42 / 546 (7.69%)	
occurrences (all)	94	75	
Musculoskeletal pain			
subjects affected / exposed	25 / 554 (4.51%)	16 / 546 (2.93%)	
occurrences (all)	31	22	
Myalgia			
subjects affected / exposed	30 / 554 (5.42%)	8 / 546 (1.47%)	
occurrences (all)	38	9	
Pain in extremity			

subjects affected / exposed occurrences (all)	47 / 554 (8.48%) 91	37 / 546 (6.78%) 68	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	29 / 554 (5.23%) 35	26 / 546 (4.76%) 32	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	68 / 554 (12.27%) 91	80 / 546 (14.65%) 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.
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 mL/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.
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.
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