Clinical trial results:
A Phase 1 Study of Eribulin Mesylate, a Novel Microtubule Targeting Chemotherapeutic Agent in Children with Refractory or Recurrent Solid Tumors (Excluding CNS), Including Lymphomas

Summary

EudraCT number	2016-001894-34
Trial protocol	Outside EU/EEA
Global end of trial date	28 January 2016

Results information

Result version number	v1 (current)
This version publication date	05 July 2018
First version publication date	05 July 2018

Trial information

Trial identification

Sponsor protocol code	E7389-A001-113

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02171260
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Eisai Medical Information, Eisai Inc., 1 8882742378, esi_medinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., 1 8882742378, esi_medinfo@eisai.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001261-PIP01-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D), to define and describe toxicities, and to characterize pharmacokinetics (PK) of eribulin mesylate administered as an intravenous infusion on Day 1 and Day 8 of a 21-day cycle to children with refractory or recurrent solid tumors (excluding central nervous system [CNS]), including lymphomas.

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	31 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	23
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	7
Adolescents (12-17 years)	16
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 18 investigative sites in the United States from 31 July 2014 to 28 January 2016.

Pre-assignment

Screening details:

In Part A1, a total of 23 subjects of greater than or equal to (>=) 12 months were enrolled, of which 22 were treated in the study. In Part A2, the study was open for the enrolment of infant subjects of less than 12 months of age, however no subjects were enrolled into this part.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Part A1: Eribulin Mesylate 1.1 mg/m^2

Arm description:

Subjects received eribulin mesylate (E7389) 1.1 milligram per square meter (mg/m^2), intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 4 cycles, or until progressive disease (PD) or unacceptable toxicity or drug related dose-limiting toxicities (DLT's).

Arm type	Experimental
Investigational medicinal product name	Eribulin Mesylate 1.1 mg/m^2
Investigational medicinal product code	
Other name	E7389
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin mesylate 1.1 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 4 cycles, or until PD or unacceptable toxicity or DLT's.

Arm title	Part A1: Eribulin Mesylate 1.4 mg/m^2

Arm description:

Subjects received eribulin mesylate 1.4 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 8 cycles, or until PD or unacceptable toxicity or drug related DLT's.

Arm type	Experimental
Investigational medicinal product name	Eribulin Mesylate 1.4 mg/m^2
Investigational medicinal product code	
Other name	E7389
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin mesylate 1.4 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 4 cycles, or until PD or unacceptable toxicity or DLT's.

Arm title	Part A1: Eribulin Mesylate 1.8 mg/m^2

Arm description:

Subjects received eribulin mesylate 1.8 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 5 cycles, or until PD or unacceptable toxicity or drug related DLT's.

Arm type	Experimental

Investigational medicinal product name	Eribulin Mesylate 1.8 mg/m^2
Investigational medicinal product code	
Other name	E7389
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin mesylate 1.8 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 4 cycles, or until PD or unacceptable toxicity or DLT's.

Arm title	Part A1: Eribulin Mesylate PK Expansion

Arm description:

Subjects received eribulin mesylate 1.4 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 2 cycles, or until PD or unacceptable toxicity or drug related DLT's for evaluation of pharmacokinetics (PK).

Arm type	Experimental
Investigational medicinal product name	Eribulin Mesylate 1.4 mg/m^2
Investigational medicinal product code	
Other name	E7389
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin mesylate 1.4 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 2 cycles, or until PD or unacceptable toxicity or drug related DLT's for evaluation of PK in PK expansion group.

Number of subjects in period 1	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2
Started	6	6	5
Completed	0	0	0
Not completed	6	6	5
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	1	-	-
Physician decision	1	-	1
Evidence of progressive disease	4	6	4

Number of subjects in period 1	Part A1: Eribulin Mesylate PK Expansion
Started	5
Completed	0
Not completed	5
Adverse event, serious fatal	1
Consent withdrawn by subject	-
Physician decision	-
Evidence of progressive disease	4

Baseline characteristics

Reporting groups[1]	
Reporting group title	Part A1: Eribulin Mesylate 1.1 mg/m^2
Reporting group description:	
Subjects received eribulin mesylate (E7389) 1.1 milligram per square meter (mg/m^2), intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 4 cycles, or until progressive disease (PD) or unacceptable toxicity or drug related dose-limiting toxicities (DLT's).	
Reporting group title	Part A1: Eribulin Mesylate 1.4 mg/m^2
Reporting group description:	
Subjects received eribulin mesylate 1.4 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 8 cycles, or until PD or unacceptable toxicity or drug related DLT's.	
Reporting group title	Part A1: Eribulin Mesylate 1.8 mg/m^2
Reporting group description:	
Subjects received eribulin mesylate 1.8 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 5 cycles, or until PD or unacceptable toxicity or drug related DLT's.	
Reporting group title	Part A1: Eribulin Mesylate PK Expansion
Reporting group description:	
Subjects received eribulin mesylate 1.4 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 2 cycles, or until PD or unacceptable toxicity or drug related DLT's for evaluation of pharmacokinetics (PK).	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 23 subjects, only 22 subjects were treated in the study. The one subject that was enrolled but not treated came off study prior to the initiation of any protocol prescribed therapy and withdrew consent.

Reporting group values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2
Number of subjects	6	6	5
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	14	10.7	13
standard deviation	± 3.52	± 2.25	± 3.24
Gender categorical			
Units: Subjects			
Female	1	4	3
Male	5	2	2

Ethnicity Units: Subjects			
Hispanic or Latino	0	2	1
Not Hispanic or Latino	6	4	4
Race Units: Subjects			
Black or African American	1	0	1
White	5	5	4
Unknown or Not Reported	0	1	0

Reporting group values	Part A1: Eribulin Mesylate PK Expansion	Total	
Number of subjects	5	22	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	12.6		
standard deviation	± 5.50	-	
Gender categorical Units: Subjects			
Female	2	10	
Male	3	12	
Ethnicity Units: Subjects			
Hispanic or Latino	1	4	
Not Hispanic or Latino	4	18	
Race Units: Subjects			
Black or African American	1	3	
White	2	16	
Unknown or Not Reported	2	3	

End points

End points reporting groups

Reporting group title	Part A1: Eribulin Mesylate 1.1 mg/m^2

Reporting group description:

Subjects received eribulin mesylate (E7389) 1.1 milligram per square meter (mg/m^2), intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 4 cycles, or until progressive disease (PD) or unacceptable toxicity or drug related dose-limiting toxicities (DLT's).

Reporting group title	Part A1: Eribulin Mesylate 1.4 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 8 cycles, or until PD or unacceptable toxicity or drug related DLT's.

Reporting group title	Part A1: Eribulin Mesylate 1.8 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.8 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 5 cycles, or until PD or unacceptable toxicity or drug related DLT's.

Reporting group title	Part A1: Eribulin Mesylate PK Expansion

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 2 cycles, or until PD or unacceptable toxicity or drug related DLT's for evaluation of pharmacokinetics (PK).

Subject analysis set title	Part A1: All Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The dose evaluable set (DES) included all subjects who were judged as DLT evaluable as recorded in the database. In order to be DLT evaluable, all subjects had to complete Cycle 1.

Primary: Maximum Tolerated Dose (MTD) of Eribulin Mesylate

End point title	Maximum Tolerated Dose (MTD) of Eribulin Mesylate[1]

End point description:

MTD: maximum dose at which <one third subjects had DLT in Cycle 1. DLT: Grade 3/4 drug-related non hematological toxicity (except Grade 3 nausea, vomiting of <3 days, Grade 3 liver enzyme elevation with alanine transaminase/aspartate transaminase and gamma glutamyl transferase that returned to Grade <=1 or baseline prior to next dose; Grade 3 fever, infection, hypophosphatemia, hypokalemia, hypocalcemia/hypomagnesemia responsive to oral supplementation). Non-hematological toxicity causing >=14 days delay between treatment cycles. Haematological DLTs included: Grade 4 neutropenia/platelets<75,000/mm^3 on Day 8 that does not resolve to absolute neutrophil count >=750/mm^3 and platelets >=75,000/mm^3 by Day 11, neutropenia for >7 days; platelet count <25,000/mm^3, or required platelet transfusion, on 2 separate days within 7-day period; Grade 3 thrombocytopenia complicated by bleeding and/or required platelet transfusion; myelosuppression causing >14 days delay between treatment cycles.

End point type	Primary

End point timeframe:

First dose of study drug (Baseline) up to Cycle 1 Day 21

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 analyzed for this endpoint.

End point values	Part A1: All Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: mg/m^2				
number (not applicable)	1.4			

Statistical analyses

No statistical analyses for this end point

Primary: 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)[2]

End point description:

TEAEs were defined as those adverse events (AEs) that occurred (or worsened, if present at Baseline) after the first dose of study drug through 30 days after the last dose of study drug. An AE was defined as any untoward medical occurrence in a subjects or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with medicinal product. A SAE was defined as any AE if it resulted in death or life-threatening AE or required inpatient hospitalization or prolongation of existing hospitalization or resulted in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions or was a congenital anomaly/birth defect. The safety analysis set (SAS) included all subjects who received at least one dose of study drug.

End point type	Primary

End point timeframe:

First dose of study drug (Baseline up to 30 days after last dose of study drug (Cycle 8 Day 38)

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 analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	5
Units: Subjects				
TEAEs	6	6	5	5
SAEs	2	1	3	4

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Change From Baseline in Clinical Laboratory Values

End point title	Number of Subjects With Clinically Significant Change From Baseline in Clinical Laboratory Values[3]

End point description:

The SAS included all subjects who received at least one dose of study drug.

End point type	Primary

End point timeframe:

First dose of study drug (Baseline) up to 30 days after last dose of study drug (Cycle 8 Day 38)

Notes:

[3] - 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 analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	5
Units: Subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Vital Sign Values

End point title	Number of Subjects With Clinically Significant Vital Sign

End point description:

The SAS included all subjects who received at least one dose of study drug.

End point type	Primary

End point timeframe:

First dose of study drug (Baseline) up to 30 days after last dose of study drug (Cycle 8 Day 38)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	5
Units: Subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Electrocardiogram (EKG)

End point title	Number of Subjects With Clinically Significant Electrocardiogram (EKG)[5]

End point description:

The SAS included all subjects who received at least one dose of study drug.

End point type	Primary

End point timeframe:

First dose of study drug (Baseline) up to 30 days after last dose of study drug (Cycle 8 Day 38)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	5
Units: Subjects				
> 30 millisecond (msec)	1	1	1	0
>60 msec	0	1	0	0

Statistical analyses

No statistical analyses for this end point

Primary: T 1/2: Terminal Half-life for Eribulin Mesylate

End point title	T 1/2: Terminal Half-life for Eribulin Mesylate[6]

End point description:

The pharmacokinetic analysis set (PAS) included all subjects who had sufficient PK data to derive at least one PK parameter. The PAS where data at specified time points was available.

End point type	Primary

End point timeframe:

Day 1 predose and at 10, 30 minutes, 1, 2, 4, 6, 24, 48, 72, 96 or 120 hours post-dose

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	5	4
Units: hours				
median (full range (min-max))	37 (29.6 to 38.9)	38.60 (23.3 to 44.3)	44.00 (30.6 to 56.5)	33.25 (30.2 to 45.9)

Statistical analyses

No statistical analyses for this end point

Primary: Cmax: Maximum Observed Plasma Concentration for Eribulin Mesylate

End point title	Cmax: Maximum Observed Plasma Concentration for Eribulin Mesylate[7]

End point description:

The PAS included all subjects who had sufficient PK data to derive at least one PK parameter.

End point type	Primary

End point timeframe:

Day 1 predose and at 10, 30 minutes, 1, 2, 4, 6, 24, 48, 72, 96 or 120 hours post-dose

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	5
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	353.8 (± 59.24)	472.3 (± 158.23)	382.6 (± 296.97)	382.8 (± 247.05)

Statistical analyses

No statistical analyses for this end point

Primary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Eribulin Mesylate

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) for Eribulin Mesylate[8]

End point description:

The PAS included all subjects who had sufficient PK data to derive at least one PK parameter.

End point type	Primary

End point timeframe:

Day 1 predose and at 10, 30 minutes, 1, 2, 4, 6, 24, 48, 72, 96 or 120 hours post-dose

Notes:

[8] - 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 analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	5
Units: hours				
median (full range (min-max))	0.170 (0.12 to 0.32)	0.170 (0.12 to 0.22)	0.370 (0.08 to 0.50)	0.300 (0.17 to 0.32)

Statistical analyses

No statistical analyses for this end point

Primary: AUC 0-t: Area Under the Concentration-time Curve From Zero (Pre-dose) to Time of Last Quantifiable Concentration for Eribulin Mesylate

End point title	AUC 0-t: Area Under the Concentration-time Curve From Zero (Pre-dose) to Time of Last Quantifiable Concentration for Eribulin Mesylate[9]

End point description:

The PAS included all subjects who had sufficient PK data to derive at least one PK parameter.

End point type	Primary

End point timeframe:

Day 1 predose and at 10, 30 minutes, 1, 2, 4, 6, 24, 48, 72, 96 or 120 hours post-dose

Notes:

[9] - 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 analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	5
Units: hour*nanogram per milliliter (h*ng/mL)				
arithmetic mean (standard deviation)	744.0 (± 353.03)	758.2 (± 303.38)	1363.0 (± 1378.53)	1010.8 (± 538.94)

Statistical analyses

No statistical analyses for this end point

Primary: AUC 0-inf: Area Under the Concentration-time Curve From Zero (Pre-dose) Extrapolated to Infinite Time for Eribulin Mesylate

End point title	AUC 0-inf: Area Under the Concentration-time Curve From Zero (Pre-dose) Extrapolated to Infinite Time for Eribulin Mesylate[10]

End point description:

The PAS included all subjects who had sufficient PK data to derive at least one PK parameter. The PAS where data at specified time points was available.

End point type	Primary

End point timeframe:

Day 1 predose and at 10, 30 minutes, 1, 2, 4, 6, 24, 48, 72, 96 or 120 hours post-dose

Notes:

[10] - 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 analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	5	4
Units: h*ng/mL				
arithmetic mean (standard deviation)	654.3 (± 342.72)	830.5 (± 331.14)	1556.6 (± 1619.37)	907.8 (± 493.59)

Statistical analyses

No statistical analyses for this end point

Primary: CL: Clearance for Eribulin Mesylate

End point title	CL: Clearance for Eribulin Mesylate[11]

End point description:

The PAS included all subjects who had sufficient PK data to derive at least one PK parameter. The PAS where data at specified timepoints was available.

End point type	Primary

End point timeframe:

Day 1 predose and at 10, 30 minutes, 1, 2, 4, 6, 24, 48, 72, 96 or 120 hours post-dose

Notes:

[11] - 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 analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	5	4
Units: milliliter per hour (mL/h)				
arithmetic mean (standard deviation)	2226.7 (± 957.10)	1951.7 (± 469.27)	2483.8 (± 1190.94)	2348.8 (± 1437.56)

Statistical analyses

No statistical analyses for this end point

Primary: Vd: Volume of Distribution for Eribulin Mesylate

End point title	Vd: Volume of Distribution for Eribulin Mesylate[12]

End point description:

The PAS included all subjects who had sufficient PK data to derive at least one PK parameter. The PAS

where data at pacified timepoints was available.

End point type	Primary

End point timeframe:

Day 1 predose and at 10, 30 minutes, 1, 2, 4, 6, 24, 48, 72, 96 or 120 hours post-dose

Notes:

[12] - 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 analyzed for this endpoint.

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	5	4
Units: milliliter				
arithmetic mean (standard deviation)	75966.7 (± 34322.34)	66766.7 (± 32230.40)	89840.0 (± 43363.96)	77525.0 (± 39176.64)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Best Overall Response

End point title	Number of Subjects With Best Overall Response

End point description:

Best Overall Response (BOR): best response recorded from start of study treatment until disease progression (PD) or recurrence based on response evaluation criteria in solid tumors (RECIST) 1.1 for target and non-target lesions. Subjects with evaluable disease were also eligible for assessment.

End point type	Secondary

End point timeframe:

First dose of study drug (Baseline) up to approximately Cycle 8 (21-days treatment cycle)

End point values	Part A1: Eribulin Mesylate 1.1 mg/m^2	Part A1: Eribulin Mesylate 1.4 mg/m^2	Part A1: Eribulin Mesylate 1.8 mg/m^2	Part A1: Eribulin Mesylate PK Expansion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	5
Units: Subjects				
SD	1	1	1	0
PR	1	0	0	0

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 (Cycle 8 Day 38)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Part A1: Eribulin Mesylate 1.1 mg/ m^2
Reporting group description:	
Subjects received eribulin mesylate 1.1 milligram mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 4 cycles, or until PD or unacceptable toxicity or DLT's.	
Reporting group title	Part A1: Eribulin Mesylate 1.4 mg/ m^2
Reporting group description:	
Subjects received eribulin mesylate 1.4 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 8 cycles, or until PD or unacceptable toxicity or drug related DLT's.	
Reporting group title	Part A1: Eribulin Mesylate 1.8 mg/ m^2
Reporting group description:	
Subjects received eribulin mesylate 1.8 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 5 cycles, or until PD or unacceptable toxicity or drug related DLT's.	
Reporting group title	Part A1: Eribulin Mesylate PK Expansion
Reporting group description:	
Subjects received eribulin mesylate 1.8 mg/m^2, intravenously over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle for up to 2 cycles, or until PD or unacceptable toxicity or drug related DLT's for evaluation of PK.	

Serious adverse events	Part A1: Eribulin Mesylate 1.1 mg/ m^2	Part A1: Eribulin Mesylate 1.4 mg/ m^2	Part A1: Eribulin Mesylate 1.8 mg/ m^2
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	3 / 5 (60.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hypoaesthesia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gingival pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachypnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part A1: Eribulin Mesylate PK Expansion		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Febrile neutropenia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fatigue				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gingival pain				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	2 / 5 (40.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Laryngeal haemorrhage				

subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachypnoea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part A1: Eribulin Mesylate 1.1 mg/ m^2	Part A1: Eribulin Mesylate 1.4 mg/ m^2	Part A1: Eribulin Mesylate 1.8 mg/ m^2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Hypotension			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	3	1	2
Malaise			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Non-cardiac chest pain			
subjects affected / exposed	2 / 6 (33.33%)	4 / 6 (66.67%)	1 / 5 (20.00%)
occurrences (all)	2	4	1
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	2 / 5 (40.00%)
occurrences (all)	0	2	2

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	3 / 6 (50.00%)	1 / 5 (20.00%)
occurrences (all)	1	4	1
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	2 / 5 (40.00%)
occurrences (all)	4	4	2
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	2 / 5 (40.00%)
occurrences (all)	6	3	2
Blood albumin decreased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Blood bilirubin increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Blood calcium decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Blood chloride decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Blood creatinine increased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Blood glucose decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Blood phosphorus decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood potassium decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	0	1	2
Blood sodium decreased			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	0 / 5 (0.00%)
occurrences (all)	4	2	0
Blood urine present			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Haemoglobin decreased			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	4 / 5 (80.00%)
occurrences (all)	5	5	6
Lymphocyte count decreased			
subjects affected / exposed	4 / 6 (66.67%)	3 / 6 (50.00%)	3 / 5 (60.00%)
occurrences (all)	6	11	7
Neutrophil count decreased			
subjects affected / exposed	5 / 6 (83.33%)	2 / 6 (33.33%)	4 / 5 (80.00%)
occurrences (all)	10	6	7
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	4 / 5 (80.00%)
occurrences (all)	1	10	6
Protein urine present			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	2	1	0

Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	2	1	2
White blood cell count decreased			
subjects affected / exposed	5 / 6 (83.33%)	5 / 6 (83.33%)	5 / 5 (100.00%)
occurrences (all)	10	15	8
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	3 / 5 (60.00%)
occurrences (all)	3	4	4
Hypoaesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 6 (66.67%)	4 / 6 (66.67%)	2 / 5 (40.00%)
occurrences (all)	6	6	5
Lymphopenia			

subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	1 / 5 (20.00%)
occurrences (all)	1	3	1
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 5 (20.00%)
occurrences (all)	0	3	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Constipation			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	3 / 5 (60.00%)
occurrences (all)	3	5	3
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Dyspepsia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	4 / 5 (80.00%)
occurrences (all)	3	7	5
Vomiting			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	2 / 5 (40.00%)
occurrences (all)	4	2	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	3 / 5 (60.00%)
occurrences (all)	1	3	4
Dry skin			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Pruritus			

subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	2 / 5 (40.00%)
occurrences (all)	1	0	2
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 5 (40.00%)
occurrences (all)	1	1	2
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	0 / 5 (0.00%)
occurrences (all)	2	3	0
Neck pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 6 (50.00%)	4 / 6 (66.67%)	2 / 5 (40.00%)
occurrences (all)	4	5	2
Hyperglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	1 / 5 (20.00%)
occurrences (all)	1	2	1
Hypermagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Hypoalbuminaemia			

subjects affected / exposed	1 / 6 (16.67%)	3 / 6 (50.00%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Hypocalcaemia			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	1 / 5 (20.00%)
occurrences (all)	1	2	1
Hypoglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Hyponatraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1

Non-serious adverse events	Part A1: Eribulin Mesylate PK Expansion		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Malaise			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Blood albumin decreased			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Blood bilirubin increased			

subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Blood calcium decreased				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Blood chloride decreased				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Blood glucose decreased				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Blood phosphorus decreased				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	2			
Blood potassium decreased				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Blood sodium decreased				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Blood urine present				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Electrocardiogram QT prolonged				
subjects affected / exposed	2 / 5 (40.00%)			
occurrences (all)	2			
Haemoglobin decreased				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Lymphocyte count decreased				
subjects affected / exposed	4 / 5 (80.00%)			
occurrences (all)	7			
Neutrophil count decreased				

subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	3		
Platelet count decreased			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	3		
Protein urine present			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	4 / 5 (80.00%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	2		
Hypoaesthesia			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Paraesthesia			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	4		
Lymphopenia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		

Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Hypermagnesaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 3		
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2		
Hyponatraemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2015	Amendment 01: The protocol was amended to update the schedule for the pharmacokinetic studies and the Day 8 dose modification guidelines following discussions with the IND Sponsor, Eisai Inc.
27 January 2016	Amendment 02: The Protocol has been amended to reflect modified risk information for eribulin. The list of toxicities in the protocol and the risk profile in the ICD have been updated to confirm to CAEPR Version 2.6, March 23, 2016 and have been adapted from this CAEPR version for our company-sponsored trial and includes risk revisions as required by the drug company.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

In Part A2, the study was open for the enrollment of infant subjects of less than 12 months of age, however no subjects were enrolled into this part.

Notes: