Clinical trial results:
A Phase 2, Multicenter, Open-label Study to Assess Safety and Preliminary Activity of Eribulin Mesylate in Pediatric Subjects With Relapsed/Refractory Rhabdomyosarcoma (RMS), Non-rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS) and Ewing Sarcoma (EWS)

Summary

EudraCT number	2018-001282-17
Trial protocol	Outside EU/EEA
Global end of trial date	21 January 2022

Results information

Result version number	v1 (current)
This version publication date	30 June 2022
First version publication date	30 June 2022

Trial information

Trial identification

Sponsor protocol code	E7389-G000-223

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03441360
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai, Inc.
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, New Jersey, United States, 07677
Public contact	Eisai Medical Information, Eisai, Inc., +1 8882742378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai, Inc., +1 8882742378, esi_oncmedinfo@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 January 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will be conducted as an assessment of the safety and preliminary activity of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS to determine whether each cohort warrants further investigation.

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 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country, and Title 21 of the United States Code of Federal
Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 April 2018
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: 21
Worldwide total number of subjects	21
EEA total number of subjects	0

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)	8
Adolescents (12-17 years)	13
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 38 investigative sites in the United States from 17 April 2018 to 21 January 2022.

Pre-assignment

Screening details:

A total of 24 subjects were screened, of which 1 was screen failure and 23 subjects were enrolled, out of which 21 subjects were enrolled and treated in the study and 2 were not treated due to withdrawal of consent and rapid disease progression (1 subject from each arm).

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?	Yes
Arm title	Eribulin mesylate 1.4 mg/m^2: RMS

Arm description:

Pediatric subjects with RMS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 milligrams per meter square (mg/m^2). Subjects continued to receive study therapy until progression of disease, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Eribulin mesylate
Investigational medicinal product code	E7389
Other name	Eribulin Halaven
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin mesylate administered as an intravenous (IV) infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2.

Arm title	Eribulin mesylate 1.4 mg/m^2: NRSTS

Arm description:

Pediatric subjects with NRSTS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2. Subjects continued to receive study therapy until progression of disease, (per RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Eribulin mesylate
Investigational medicinal product code	E7389
Other name	Eribulin Halaven
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin mesylate administered as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2.

Arm title	Eribulin mesylate 1.4 mg/m^2: EWS

Arm description:

Pediatric subjects with EWS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day

cycle at a dose of 1.4 mg/m^2. Subjects continued to receive study therapy until progression of disease, (per RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Eribulin mesylate
Investigational medicinal product code	E7389
Other name	Eribulin Halaven
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eribulin mesylate administered as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2.

Number of subjects in period 1	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS
Started	8	8	5
Completed	0	0	0
Not completed	8	8	5
Adverse event, non-fatal	1	-	1
Clinical disease progression	2	2	-
Radiological disease progression	5	6	4

Baseline characteristics

Reporting groups	
Reporting group title	Eribulin mesylate 1.4 mg/m^2: RMS
Reporting group description:	
Pediatric subjects with RMS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 milligrams per meter square (mg/m^2). Subjects continued to receive study therapy until progression of disease, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.	
Reporting group title	Eribulin mesylate 1.4 mg/m^2: NRSTS
Reporting group description:	
Pediatric subjects with NRSTS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2. Subjects continued to receive study therapy until progression of disease, (per RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.	
Reporting group title	Eribulin mesylate 1.4 mg/m^2: EWS
Reporting group description:	
Pediatric subjects with EWS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2. Subjects continued to receive study therapy until progression of disease, (per RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.	

Reporting group values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS
Number of subjects	8	8	5
Age categorical			
Units: subjects			
Age Continuous			
Units: years			
arithmetic mean	10.4	11.8	13.2
standard deviation	± 4.53	± 5.57	± 4.32
Sex: Female, Male			
Units: subjects			
Female	2	4	1
Male	6	4	4
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	1
White	5	4	2
More than one race	0	0	0
Unknown or Not Reported	1	1	2
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	2	1
Not Hispanic or Latino	5	6	3
Unknown or Not Reported	0	0	1

Reporting group values	Total		
Number of subjects	21		
Age categorical Units: subjects			

Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: subjects			
Female	7		
Male	14		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	5		
White	11		
More than one race	0		
Unknown or Not Reported	4		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6		
Not Hispanic or Latino	14		
Unknown or Not Reported	1		

End points

End points reporting groups

Reporting group title	Eribulin mesylate 1.4 mg/m^2: RMS

Reporting group description:

Pediatric subjects with RMS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 milligrams per meter square (mg/m^2). Subjects continued to receive study therapy until progression of disease, per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.

Reporting group title	Eribulin mesylate 1.4 mg/m^2: NRSTS

Reporting group description:

Pediatric subjects with NRSTS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2. Subjects continued to receive study therapy until progression of disease, (per RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.

Reporting group title	Eribulin mesylate 1.4 mg/m^2: EWS

Reporting group description:

Pediatric subjects with EWS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2. Subjects continued to receive study therapy until progression of disease, (per RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.

Primary: Percentage of Subjects With Objective Response

End point title	Percentage of Subjects With Objective Response[1]

End point description:

Percentage of subjects achieving a best objective response of partial response (PR) or complete response (CR) per RECIST 1.1, by up to 24 weeks after all subjects have completed response assessment. Response assessment was determined by investigator. CR was defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must had reduction in the short axis to less than (<) 10 millimeters (mm). PR was defined as at least a 30 percent (%) decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The FAS included all subjects who receive at least 1 dose of study drug.

End point type	Primary

End point timeframe:

From date of randomization up to first documentation of disease progression (PD) or date of death, whichever occurred first (approximately 32 months)

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: Planned analyses for these data was descriptive only.

End point values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	5	
Units: percentage of subjects				
number (confidence interval 95%)	0 (0.0 to 36.9)	0 (0.0 to 36.9)	0 (0.0 to 52.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the time from the first dose date to the date of PD or date of death (whichever occurred first). PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this included the baseline sum if that was the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions was also considered progression). The FAS included all subjects who receive at least 1 dose of study drug. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date (PCD).

End point type	Secondary

End point timeframe:

From the time from the first dose date to the date of disease progression (PD) or date of death, whichever occurred first (up to approximately 32 months)

End point values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	5	
Units: months				
median (confidence interval 95%)	1.74 (1.12 to 2.86)	1.30 (0.62 to 1.51)	0.76 (0.59 to 4.04)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An AE was any untoward medical occurrence in subject administered with an investigational product. An SAE was any untoward medical occurrence that at any dose: resulted in death; life threatening; requires subject hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug). A treatment-emergent adverse event (TEAE) was defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or (1) reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or (2) worsens in severity during treatment relative to the pretreatment state, when the AE is continuous. The safety analysis set (SAS) included all subjects who receive at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug up to approximately 44 months

End point values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	5	
Units: subjects				
TEAEs	8	8	5	
SAEs	6	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With a Shift From Baseline to Worst Post-Baseline Common Terminology Criteria for Adverse Events (CTCAE) Grade in Laboratory Value

End point title	Number of Subjects With a Shift From Baseline to Worst Post-Baseline Common Terminology Criteria for Adverse Events (CTCAE) Grade in Laboratory Value

End point description:

Laboratory results were graded using CTCAE Version 4.03. As per CTCAE, Grade 1 scales as Mild; Grade 2 scales as Moderate; Grade 3 scales as severe or medically significant but not immediately life threatening; Grade 4 scales as life-threatening consequences. The safety analysis set included all subjects who receive at least 1 dose of study drug. Here number analyzed "n" are the subjects who were evaluable for the outcome measure for given categories with non-missing data at both baseline and any post-baseline. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date.

End point type	Secondary

End point timeframe:

From first dose of study drug up to approximately 32 months

End point values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	5	
Units: subjects				
Grade 0, Hemoglobin Decreased	0	0	0	
Grade 1, Hemoglobin Decreased	3	4	3	
Grade 2, Hemoglobin Decreased	0	1	2	
Grade 3, Hemoglobin Decreased	5	3	0	
Grade 4, Hemoglobin Decreased	0	0	0	
Grade 0, Hemoglobin increased	0	0	0	
Grade 1, Hemoglobin increased	0	0	0	
Grade 2, Hemoglobin increased	0	0	0	

Grade 3, Hemoglobin increased	0	0	0	
Grade 4, Hemoglobin increased	0	0	0	
Grade 0, White blood cells decreased	0	1	0	
Grade 1, White blood cells decreased	4	2	1	
Grade 2, White blood cells decreased	2	1	0	
Grade 3, White blood cells decreased	0	2	3	
Grade 4, White blood cells decreased	2	1	1	
Grade 0, White blood cells increased	0	0	0	
Grade 1, White blood cells increased	0	0	0	
Grade 2, White blood cells increased	0	0	0	
Grade 3, White blood cells increased	0	0	0	
Grade 4, White blood cells increased	0	0	0	
Grade 0, Lymphocyte count decreased	3	2	0	
Grade 1, Lymphocyte count decreased	1	0	0	
Grade 2, Lymphocyte count decreased	1	0	3	
Grade 3, Lymphocyte count decreased	2	4	2	
Grade 4, Lymphocyte count decreased	1	0	0	
Grade 0, Lymphocyte count increased	8	4	5	
Grade 1, Lymphocyte count increased	0	0	0	
Grade 2, Lymphocyte count increased	0	2	0	
Grade 3, Lymphocyte count increased	0	0	0	
Grade 4, Lymphocyte count increased	0	0	0	
Grade 0, Neutrophil count decreased	1	0	1	
Grade 1, Neutrophil count decreased	1	0	0	
Grade 2, Neutrophil count decreased	3	1	0	
Grade 3, Neutrophil count decreased	0	1	3	
Grade 4, Neutrophil count decreased	2	5	1	
Grade 0, Platelet count decreased	5	6	3	
Grade 1, Platelet count decreased	2	1	2	
Grade 2, Platelet count decreased	1	0	0	
Grade 3, Platelet count decreased	0	0	0	
Grade 4, Platelet count decreased	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change From Baseline in Electrocardiogram (ECG) Values

End point title	Number of Subjects With Clinically Significant Change From Baseline in Electrocardiogram (ECG) Values

End point description:

The safety analysis set included all subjects who receive at least 1 dose of study drug. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date.

End point type	Secondary

End point timeframe:

From first dose of study drug up to approximately 32 months

End point values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	5	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change From Baseline in Vital Signs Values

End point title	Number of Subjects With Clinically Significant Change From Baseline in Vital Signs Values

End point description:

The safety analysis set included all subjects who receive at least 1 dose of study drug. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date.

End point type	Secondary

End point timeframe:

From first dose of study drug up to approximately 32 months

End point values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	5	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline to Worst Post-baseline for Lansky Play-performance Scale

End point title	Number of Subjects With Shift From Baseline to Worst Post-baseline for Lansky Play-performance Scale

End point description:

Reduced activities of daily living was assessed using the Lansky Play Performance Scale, where 100=fully active; 90=minor restrictions in strenuous physical activity; 80=active, gets tired more quickly; 70=greater restriction of play, less time spent in play activity; 60=up and around, active play minimal; quieter activities; 50=lying around much of the day; no active playing, all quiet play and

activities; 40=mainly in bed; quiet activities; 30=bedbound; needs assistance even for quiet play; 20=sleeps often; play limited to very passive activities; 10=doesn't play or get out of bed; 5=unresponsive 0=dead. The safety analysis set included all subjects who receive at least 1 dose of study drug. Here overall number analyzed "N" are the subjects who were evaluable for the outcome measure with non-missing data at both baseline and any post-baseline timepoint. As planned, data for this secondary endpoint was collected and analyzed up to the primary completion date.

End point type	Secondary

End point timeframe:

Baseline up to approximately 32 months

End point values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	4	
Units: subjects				
Baseline: 70 to worst post-baseline: 50	1	0	0	
Baseline: 70 to worst post-baseline: 60	0	0	0	
Baseline: 70 to worst post-baseline: 70	2	0	1	
Baseline: 70 to worst post-baseline: 80	0	0	0	
Baseline: 70 to worst post-baseline: 90	0	0	0	
Baseline: 70 to worst post-baseline: 100	0	0	0	
Baseline: 80 to worst post-baseline: 50	0	0	0	
Baseline: 80 to worst post-baseline: 60	1	0	0	
Baseline: 80 to worst post-baseline: 70	1	1	0	
Baseline: 80 to worst post-baseline: 80	0	2	1	
Baseline: 80 to worst post-baseline: 90	0	0	0	
Baseline: 80 to worst post-baseline: 100	0	0	0	
Baseline: 90 to worst post-baseline: 50	0	0	0	
Baseline: 90 to worst post-baseline: 60	0	0	1	
Baseline: 90 to worst post-baseline: 70	0	0	0	
Baseline: 90 to worst post-baseline: 80	1	0	1	
Baseline: 90 to worst post-baseline: 90	0	2	0	
Baseline: 90 to worst post-baseline: 100	0	0	0	
Baseline: 100 to worst post-baseline: 50	0	0	0	
Baseline: 100 to worst post-baseline: 60	0	0	0	
Baseline:100 to worst post-baseline: 70	1	1	0	
Baseline: 100 to worst post-baseline: 80	0	0	0	
Baseline: 100 to worst post-baseline: 90	0	0	0	
Baseline: 100 to worst post-baseline: 100	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline to Worst Post-baseline for Karnofsky Performance Status Scores

End point title	Number of Subjects With Shift From Baseline to Worst Post-baseline for Karnofsky Performance Status Scores

End point description:

Scale assessed as best/worst score change from baseline by functional impairment.Score ranges:0-100, lower score worst survival for most serious illnesses.100=normal;no complaints;no evidence of disease;90=able to carry on normal activity with effort,minor sign or symptoms of disease;80=normal activity with effort;some sign/symptoms of disease;70=cares for self;unable to carry on normal activity/do active work;60=requires occasional assistance,but is able to care for most personal needs;50=requires considerable assistance, frequent medical care;40=disabled; requires special care, assistance;30=severely disabled; hospitalization indicated, although death is not imminent;20=very sick;hospitalization;10=moribund;fatal processes progressively worsening;0=dead.The SAS included all subjects who receive at least 1 dose of study drug.“N”=subjects evaluable for OM with non-missing data at baseline; any post-baseline timepoint. Data for secondary endpoint was collected and analyzed up to PCD.

End point type	Secondary

End point timeframe:

Baseline up to approximately 32 months

End point values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	0[2]	1	
Units: subjects				
Baseline score 70 to worst post-baseline score 50	0		0	
Baseline score 70 to worst post-baseline score 60	0		0	
Baseline score 70 to worst post-baseline score 70	1		0	
Baseline score 70 to worst post-baseline score 80	0		0	
Baseline score 70 to worst post-baseline score 90	0		0	
Baseline score 90 to worst post-baseline score 50	0		0	
Baseline score 90 to worst post-baseline score 60	0		0	
Baseline score 90 to worst post-baseline score 70	0		0	
Baseline score 90 to worst post-baseline score 80	0		1	
Baseline score 90 to worst post-baseline score 90	0		0	
Baseline score 90 to worst post-baseline score 100	0		0	

Notes:

[2] - "n" signifies non-missing data at both baseline and any post-baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as the time from the first date of documented PR or CR to the date of disease progression or date of death (whichever occurred first). CR was defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must had reduction in the short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this included the baseline sum if that was the smallest on study). The FAS included all subjects who receive at least 1 dose of study drug. Here overall number analyzed "N" are the subjects who were evaluable for the OM however no subjects with best overall response of complete response or partial response were observed here. As planned, data for this secondary endpoint was collected and analyzed up to the PCD.

End point type	Secondary

End point timeframe:

From day of first documentation of PR or CR to the day of disease progression or death (up to approximately 32 months)

End point values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	0[4]	0[5]	
Units: months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[3] - No subjects with best overall response of complete response or partial response were observed here.
[4] - No subjects with best overall response of complete response or partial response were observed here.
[5] - No subjects with best overall response of complete response or partial response were observed here.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the first dose date to the date of death. The FAS included all subjects who receive at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From the day of first dose to the day of death, up to approximately 44 months

End point values	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: NRSTS	Eribulin mesylate 1.4 mg/m^2: EWS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	5	
Units: months				

median (confidence interval 95%)	5.08 (1.74 to 6.47)	6.95 (0.72 to 16.26)	7.89 (2.50 to 29.80)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of administration of first dose up to 28 days after the last dose, or until resolution, whichever came first (up to approximately 44 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Eribulin mesylate 1.4 mg/m^2: RMS

Reporting group description:

Pediatric subjects with RMS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2. Subjects continued to receive study therapy until progression of disease, (per RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.

Reporting group title	Eribulin mesylate 1.4 mg/m^2: EWS

Reporting group description:

Pediatric subjects with EWS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2. Subjects continued to receive study therapy until progression of disease, (per RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.

Reporting group title	Eribulin mesylate 1.4 mg/m^2: NRSTS

Reporting group description:

Pediatric subjects with NRSTS received eribulin mesylate as an IV infusion on Days 1 and 8 of each 21-day cycle at a dose of 1.4 mg/m^2. subjects continued to receive study therapy until progression of disease, (per RECIST v.1.1), exhibited no clinical benefit, intolerable toxicity, withdrawal of consent or termination of the study program, whichever occurred first.

Serious adverse events	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: EWS	Eribulin mesylate 1.4 mg/m^2: NRSTS
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	3 / 5 (60.00%)	2 / 8 (25.00%)
number of deaths (all causes)	8	5	7
number of deaths resulting from adverse events	1	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Malignant pleural effusion			

subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac tamponade			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (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
Left ventricular dysfunction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (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
Pericardial effusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (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
Sinus tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neuralgia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (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
Seizure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (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
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mouth haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (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
Epistaxis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (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
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (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
Costochondritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (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
Muscular weakness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Eribulin mesylate 1.4 mg/m^2: RMS	Eribulin mesylate 1.4 mg/m^2: EWS	Eribulin mesylate 1.4 mg/m^2: NRSTS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	5 / 5 (100.00%)	8 / 8 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Tumour haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Tumour pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	4 / 8 (50.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	5	1	0
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	4 / 8 (50.00%)	1 / 5 (20.00%)	4 / 8 (50.00%)
occurrences (all)	8	1	4
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Oedema peripheral			

subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	3 / 8 (37.50%)	2 / 5 (40.00%)	3 / 8 (37.50%)
occurrences (all)	4	2	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	3 / 8 (37.50%)
occurrences (all)	2	0	3
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Tracheal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			

Agitation			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Depression			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Alanine aminotransferase increased			
subjects affected / exposed	5 / 8 (62.50%)	2 / 5 (40.00%)	2 / 8 (25.00%)
occurrences (all)	9	2	2
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 8 (75.00%)	3 / 5 (60.00%)	1 / 8 (12.50%)
occurrences (all)	12	4	3
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	2 / 8 (25.00%)
occurrences (all)	3	0	3
Blood bilirubin increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	1 / 8 (12.50%)
occurrences (all)	4	1	2
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 8 (37.50%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	3	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 8 (37.50%)	2 / 5 (40.00%)	1 / 8 (12.50%)
occurrences (all)	3	3	1
International normalised ratio			

increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	3	0	1
Neutrophil count decreased			
subjects affected / exposed	7 / 8 (87.50%)	4 / 5 (80.00%)	4 / 8 (50.00%)
occurrences (all)	13	26	11
Lymphocyte count decreased			
subjects affected / exposed	3 / 8 (37.50%)	3 / 5 (60.00%)	4 / 8 (50.00%)
occurrences (all)	9	13	5
Lymphocyte count increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	1 / 8 (12.50%)
occurrences (all)	4	3	2
Protein urine present			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Weight increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	4	0	1
White blood cell count decreased			
subjects affected / exposed	6 / 8 (75.00%)	3 / 5 (60.00%)	4 / 8 (50.00%)
occurrences (all)	16	23	12
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Mitral valve disease			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Palpitations			

subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pulmonary valve disease			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Tricuspid valve disease			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	2 / 8 (25.00%)
occurrences (all)	10	0	2
Lethargy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Paraesthesia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Peripheral motor neuropathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	5 / 8 (62.50%)	4 / 5 (80.00%)	5 / 8 (62.50%)
occurrences (all)	24	16	7
Leukopenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	3 / 8 (37.50%)
occurrences (all)	0	0	6
Thrombocytopenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	2 / 8 (25.00%)
occurrences (all)	1	1	2
Diarrhoea			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	2 / 8 (25.00%)
occurrences (all)	2	0	2
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	2 / 8 (25.00%)
occurrences (all)	3	1	2
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Vomiting			

subjects affected / exposed	3 / 8 (37.50%)	1 / 5 (20.00%)	1 / 8 (12.50%)
occurrences (all)	7	1	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 8 (37.50%)	0 / 5 (0.00%)	4 / 8 (50.00%)
occurrences (all)	3	0	4
Night sweats			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Proteinuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Muscle spasms			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	3 / 8 (37.50%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

Neck pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	2 / 8 (25.00%)
occurrences (all)	3	3	3
Pain in jaw			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Catheter site infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	3 / 8 (37.50%)
occurrences (all)	2	2	3
Dehydration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Hypercalcaemia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Hyperglycaemia			
subjects affected / exposed	4 / 8 (50.00%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	12	0	0
Hyperkalaemia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Hypermagnesaemia			
subjects affected / exposed	2 / 8 (25.00%)	1 / 5 (20.00%)	1 / 8 (12.50%)
occurrences (all)	3	1	1
Hypernatraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 5 (40.00%)	0 / 8 (0.00%)
occurrences (all)	0	5	0
Hypoalbuminaemia			
subjects affected / exposed	4 / 8 (50.00%)	2 / 5 (40.00%)	1 / 8 (12.50%)
occurrences (all)	10	4	1
Hypocalcaemia			
subjects affected / exposed	3 / 8 (37.50%)	1 / 5 (20.00%)	0 / 8 (0.00%)
occurrences (all)	6	3	0
Hypokalaemia			
subjects affected / exposed	3 / 8 (37.50%)	2 / 5 (40.00%)	0 / 8 (0.00%)
occurrences (all)	4	2	0
Hyponatraemia			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	3 / 8 (37.50%)
occurrences (all)	3	3	3
Hypophosphataemia			
subjects affected / exposed	3 / 8 (37.50%)	1 / 5 (20.00%)	1 / 8 (12.50%)
occurrences (all)	5	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 July 2017	Inclusion Criterion was updated in line with the label for Halaven® regarding definition of impaired renal function. Exclusion Criterion was updated in line with the label for Halaven, regarding the concomitant use of drugs that prolong the QTc. (Eribulin mesylate, Instructions for QTc Prolongation on Electrocardiogram [ECG]) was updated in line with the Halaven label. The text regarding pregnancy testing was amended to clarify that serum beta-human chorionic gonadotropin or urine test is required within 72 hours of first dose of study drug and to align Exclusion Criterion and Schedule of Procedures/Assessments.
29 September 2017	In view of the subject population, CNS imaging was only to be required for subjects with a history of protocol-eligible brain metastasis and as clinically indicated. The text was updated for clarification purposes. Assessment grade added for NRSTS for clarification. Time of full neurological examination and assessment criteria used were modified for clarification. Instructions for prior antibody therapy were updated in line with eribulin study protocols. Clarification that for sites outside the EU, double barrier method of contraception is acceptable for those subjects that are not on a stable dose of hormonal contraception. The text was updated for clarification purposes; responses confirmed 4 weeks post initial assessment of PR/CR per RECIST v.1.1 were to be used in the analysis.
20 December 2018	Two exploratory objectives of DOR and OS were changed to secondary objectives, endpoints and analyses following feedback from the FDA and the European Medicines Agency Paediatric Committee (EMA PDCO). Inclusion Criterion was corrected. Exclusion Criterion was updated to be in line with eribulin study protocols. The screening period was extended from 14 to 28 days, following feedback from investigators, to allow more time for completion of screening procedures and to prevent unnecessary repeat scans. Following feedback from the EMA PDCO, the duration of follow-up was clarified and increased. Magnesium was added to the chemistry panel for clinical laboratory tests in line with eribulin study protocols.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported