Clinical trial results:
A Phase 1/2 Single-arm Study Evaluating the Safety and Efficacy of Eribulin Mesilate in Combination With Irinotecan in Children with Refractory or Recurrent Solid Tumors.

Summary

EudraCT number	2016-003352-67
Trial protocol	DE GB ES PL IT
Global end of trial date	17 May 2021

Results information

Result version number	v1
This version publication date	02 December 2021
First version publication date	02 December 2021

Trial information

Trial identification

Sponsor protocol code	E7389-G000-213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03245450
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., 1 888-274-2378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., 1 888-274-2378, esi_oncmedinfo@eisai.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	09 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was Phase 1: To determine the maximum tolerated dose (MTD) and Recommended Phase 2 Dose (RP2D) of eribulin mesilate in combination with weekly and daily irinotecan hydrochloride in pediatric subjects with relapsed/refractory solid tumors, excluding central nervous system (CNS); Phase 2: To assess the objective response rate (ORR) and duration of response (DOR) of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects with rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and Ewing sarcoma (EWS).

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:- Principles of the World Medical Association Declaration of Helsinki 2013; - 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 on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; - 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;- 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 SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 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	Germany: 3
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	40
EEA total number of subjects	35

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)	20
Adolescents (12-17 years)	20
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 22 investigative sites in France, Germany, Greece, Italy, Poland, Spain and United Kingdom.

Pre-assignment

Screening details:

A total of 46 subjects were screened and signed inform consent form, of which 13 subjects were treated in the Phase 1 and 27 subjects were treated in Phase 2.

Period 1

Period 1 title	Overall (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	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2

Arm description:

Subjects received eribulin mesylate 1.4 milligram per square meter (mg/m^2) intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 20 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of dose limiting toxicities (DLTs) in cycle 1.

Arm type	Experimental
Investigational medicinal product name	Irinotecan 20 mg/m^2
Investigational medicinal product code	
Other name	Irinotecan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received irinotecan hydrochloride 20 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle.

Investigational medicinal product name	Eribulin Mesilate 1.4 mg/m^2
Investigational medicinal product code	
Other name	E7389, HALAVEN
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 in a 21 day treatment cycle.

Arm title	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2

Arm description:

Subjects received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Arm type	Experimental

Investigational medicinal product name	Irinotecan 40 mg/m^2
Investigational medicinal product code	
Other name	Irinotecan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle.

Investigational medicinal product name	Eribulin Mesilate 1.4 mg/m^2
Investigational medicinal product code	
Other name	E7389, HALAVEN
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 in a 21 day treatment cycle.

Arm title	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2

Arm description:

Subjects received eribulin mesylate 1.4 mg/m^2 and irinotecan hydrochloride 100 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Arm type	Experimental
Investigational medicinal product name	Irinotecan 100 mg/m^2
Investigational medicinal product code	
Other name	Irinotecan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received irinotecan hydrochloride 100 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle.

Investigational medicinal product name	Eribulin Mesilate 1.4 mg/m^2
Investigational medicinal product code	
Other name	E7389, HALAVEN
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received eribulin mesylate 1.4 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle.

Arm title	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2

Arm description:

Subjects received eribulin mesylate 1.4 mg/m^2 and irinotecan hydrochloride 125 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Arm type	Experimental
Investigational medicinal product name	Irinotecan 125 mg/m^2
Investigational medicinal product code	
Other name	Irinotecan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received irinotecan hydrochloride 125 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle.

Investigational medicinal product name	Eribulin Mesilate 1.4 mg/m^2
Investigational medicinal product code	
Other name	E7389, HALAVEN
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received eribulin mesylate 1.4 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle.

Arm title	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2

Arm description:

Subjects with RMS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Arm type	Experimental
Investigational medicinal product name	Irinotecan 40 mg/m^2
Investigational medicinal product code	
Other name	Irinotecan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with RMS received irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (39 months).

Investigational medicinal product name	Eribulin Mesilate 1.4 mg/m^2
Investigational medicinal product code	
Other name	E7389, HALAVEN
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with RMS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (39 months).

Arm title	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2

Arm description:

Subjects with NRSTS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Arm type	Experimental
Investigational medicinal product name	Irinotecan 40 mg/m^2
Investigational medicinal product code	
Other name	Irinotecan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with NRSTS received irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (39 months).

Investigational medicinal product name	Eribulin Mesilate 1.4 mg/m^2
Investigational medicinal product code	
Other name	E7389, HALAVEN
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with NRSTS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (39 months).

Arm title	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2

Arm description:

Subjects with EWS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and Irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Arm type	Experimental
Investigational medicinal product name	Irinotecan 40 mg/m^2
Investigational medicinal product code	
Other name	Irinotecan
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with EWS received irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (39 months).

Investigational medicinal product name	Eribulin Mesilate 1.4 mg/m^2
Investigational medicinal product code	
Other name	E7389, HALAVEN
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects with EWS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (39 months).

Number of subjects in period 1	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2
Started	3	4	3
Completed	0	0	0
Not completed	3	4	3
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	-	1	-
Not specified	-	-	-
Clinical disease progression	-	-	1
Radiological disease progression	3	3	2

Number of subjects in period 1	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2
Started	3	9	9

Completed	0	0	0
Not completed	3	9	9
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	-	-	-
Not specified	1	1	1
Clinical disease progression	-	-	2
Radiological disease progression	2	7	6

Number of subjects in period 1	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2
Started	9
Completed	0
Not completed	9
Adverse event, serious fatal	2
Consent withdrawn by subject	-
Not specified	1
Clinical disease progression	-
Radiological disease progression	6

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 milligram per square meter (mg/m^2) intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 20 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of dose limiting toxicities (DLTs) in cycle 1.

Reporting group title	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Reporting group title	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2 and irinotecan hydrochloride 100 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Reporting group title	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2 and irinotecan hydrochloride 125 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Reporting group title	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2

Reporting group description:

Subjects with RMS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Reporting group title	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2

Reporting group description:

Subjects with NRSTS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Reporting group title	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2

Reporting group description:

Subjects with EWS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and Irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Reporting group values	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2
Number of subjects	3	4	3
Age Categorical Units: Subjects			
In utero	0	0	0

Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	1	4	1
Adolescents (12-17 years)	2	0	2
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	10.94	7.33	13.97
standard deviation	± 6.583	± 2.540	± 4.231
Gender Categorical			
Units: Subjects			
Male	1	3	1
Female	2	1	2
Race			
Units: Subjects			
White	3	4	2
Asian	0	0	1
Black or African American	0	0	0
Other	0	0	0
Missing	0	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	3	3	3

Reporting group values	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2
Number of subjects	3	9	9
Age Categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	2	5	3
Adolescents (12-17 years)	1	4	6
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	8.06	11.05	12.71
standard deviation	± 4.9997	± 3.845	± 4.348

Gender Categorical Units: Subjects			
Male	1	4	7
Female	2	5	2
Race Units: Subjects			
White	3	5	8
Asian	0	0	1
Black or African American	0	0	0
Other	0	2	0
Missing	0	2	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	3	9	8

Reporting group values	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	Total	
Number of subjects	9	40	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	4	20	
Adolescents (12-17 years)	5	20	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	11.59		
standard deviation	± 3.753	-	
Gender Categorical Units: Subjects			
Male	4	21	
Female	5	19	
Race Units: Subjects			
White	8	33	
Asian	0	2	
Black or African American	0	0	
Other	0	2	
Missing	1	3	
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	

Not Hispanic or Latino	9	38	

End points

End points reporting groups

Reporting group title	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 milligram per square meter (mg/m^2) intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 20 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of dose limiting toxicities (DLTs) in cycle 1.

Reporting group title	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Reporting group title	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2 and irinotecan hydrochloride 100 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Reporting group title	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2 and irinotecan hydrochloride 125 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Reporting group title	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2

Reporting group description:

Subjects with RMS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Reporting group title	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2

Reporting group description:

Subjects with NRSTS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Reporting group title	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2

Reporting group description:

Subjects with EWS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and Irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Subject analysis set title	Phase 1: All Subjects (Dose Evaluable Set)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects received eribulin mesylate 1.4 mg/m^2 intravenous infusion on Days 1 and 8 (schedule A and B) and irinotecan hydrochloride 20 mg/m^2 or 40 mg/m^2 intravenous infusion on Days 1 to 5 (schedule A) and irinotecan hydrochloride 100 mg/m^2 or 125 mg/m^2 intravenous infusion on Days 1 and 8 (schedule B) in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of dose limiting toxicities (DLTs) in cycle 1. Dose Evaluable Set (DES) was used for evaluation of each dose level for dose escalation and for determination of MTD.

Primary: Phase 1: Maximum Tolerated Dose (MTD) of Eribulin Mesylate in Combination with Irinotecan Hydrochloride

End point title	Phase 1: Maximum Tolerated Dose (MTD) of Eribulin Mesylate in Combination with Irinotecan Hydrochloride[1]

End point description:

The MTD was defined as the highest dose level at which less than 1/3 of subjects experience a DLT during Cycle 1 of therapy. DES for Phase 1 included all subjects who completed Cycle 1 treatment and were evaluated for DLT, and those who discontinued during Cycle 1 due to DLT. DES was used for evaluation of each dose level for dose escalation and for determination of MTD.

End point type	Primary

End point timeframe:

First dose of study drug up to Cycle 1 (Cycle length=21 days)

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.

End point values	Phase 1: All Subjects (Dose Evaluable Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: mg/m^2				
number (not applicable)				
Eribulin Mesylate	1.4			
Irinotecan Hydrochloride	40			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Objective response rate (ORR)

End point title	Phase 2: Objective response rate (ORR)[2][3]

End point description:

ORR was defined as the percentage of subjects with a best overall response (BOR) of confirmed partial response (PR) or complete response (CR) determined by investigator assessment per Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. CR was disappearance of all target and non-target lesions. All pathological (whether target or non-target) must have a reduction in their short axis less than (<) 10 millimeter (mm). PR was at least a 30 percent (%) decrease in the sum of diameter (SOD) of target lesions, taking as reference the baseline sum diameters. Full analysis set included subjects who received at least 1 dose of either study drug.

End point type	Primary

End point timeframe:

From date of first dose of study drug until disease progression, development of unacceptable toxicity, withdrawal of consent, or up to approximately 3 years 3 months

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.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was assessed in Phase 2 only.

End point values	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	9	
Units: percentage of subjects				
number (confidence interval 90%)	11.1 (0.6 to 42.9)	11.1 (0.6 to 42.9)	11.1 (0.6 to 42.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point description:

A TEAE was defined as an AE that emerged during treatment, having been absent at pretreatment, or reemerged during treatment, having been present at pre-treatment (baseline) but stopped before treatment, or worsened in severity during treatment relative to the pretreatment state, when the AE was continuous. AE was defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. Safety Analysis Set included subjects who received at least 1 dose of either study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug up to approximately 3 years 3 months

End point values	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	3
Units: subjects	3	4	3	3

End point values	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	9	
Units: subjects	9	9	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serious Adverse Event (SAE)

End point title	Number of Subjects With Serious Adverse Event (SAE)

End point description:

SAE was defined as any untoward medical occurrence at any dose 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. Safety analysis set included subjects who received at least 1 dose of either study drug.

End point type	Secondary

End point timeframe:

Up to approximately 3 years and 3 months

End point values	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	3
Units: subjects	1	3	0	1

End point values	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	9	
Units: subjects	5	4	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1, Cmax: Maximum Observed Plasma Concentration of Eribulin,

Irinotecan and its Active Metabolite SN-38

End point title	Phase 1, Cmax: Maximum Observed Plasma Concentration of Eribulin, Irinotecan and its Active Metabolite SN-38[4]

End point description:

Pharmacokinetic analysis set included subjects who had documented dosing history and at least one post-dosing quantifiable drug concentration.

End point type	Secondary

End point timeframe:

For eribulin, Cycle 1 Day 1: 0-120 hours post-eribulin infusion; For irinotecan and its metabolite, Cycle 1 Day 1: 0-24 hours post-irinotecan infusion (cycle length=21 days)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was assessed in Phase 1 only.

End point values	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	3
Units: nanogram/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Eribulin	369.3 (± 58.0)	179.4 (± 136.1)	348.7 (± 25.0)	323.3 (± 20.6)
Irinotecan	538.8 (± 165.9)	399.5 (± 19.1)	1168.1 (± 39.8)	1555.4 (± 39.5)
Active Metabolite SN-38	6.518 (± 9.4)	17.170 (± 39.7)	25.409 (± 51.6)	18.614 (± 74.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1, Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) of Eribulin, Irinotecan and its Active Metabolite SN-38

End point title	Phase 1, Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) of Eribulin, Irinotecan and its Active Metabolite SN-38[5]

End point description:

Pharmacokinetic analysis set included subjects who had documented dosing history and at least one post-dosing quantifiable drug concentration.

End point type	Secondary

End point timeframe:

For eribulin, Cycle 1 Day 1: 0-120 hours post-eribulin infusion; For irinotecan and its metabolite, Cycle 1 Day 1: 0-24 hours post-irinotecan infusion (cycle length=21 days)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was assessed in Phase 1 only.

End point values	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	3
Units: hours				
median (full range (min-max))				
Eribulin	0.080 (0.03 to 0.22)	0.135 (0.03 to 1)	0.080 (0 to 0.12)	0.050 (0.01 to 0.12)
Irinotecan	0.250 (0.07 to 0.42)	0.305 (0 to 24)	0.300 (0.03 to 0.33)	0.170 (0.13 to 0.25)
Active Metabolite SN-38	0.420 (0.25 to 1.03)	0.305 (0 to 24)	0.330 (0.3 to 0.53)	0.250 (0.13 to 0.55)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1, T1/2: Half-life of Eribulin, Irinotecan and its Active Metabolite SN-38

End point title	Phase 1, T1/2: Half-life of Eribulin, Irinotecan and its Active Metabolite SN-38[6]

End point description:

Pharmacokinetic analysis set included subjects who had documented dosing history and at least one post-dosing quantifiable drug concentration. Here 'N' (overall number of subjects analyzed) included all subjects who were evaluable for this outcome measure and 'n' (number analyzed) included all subjects who were evaluable for each category. Here '99999' signifies that no subject was analyzed.

End point type	Secondary

End point timeframe:

For eribulin, Cycle 1 Day 1: 0-120 hours post-eribulin infusion; For irinotecan and its metabolite, Cycle 1 Day 1: 0-24 hours post-irinotecan infusion (cycle length=21 days)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was assessed in Phase 1 only.

End point values	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	2
Units: hours				
median (full range (min-max))				
Eribulin(n=3,3,3,2)	27.50 (26.5 to 27.7)	34.70 (32.9 to 40.4)	30.00 (23.4 to 43.3)	25.30 (22.1 to 28.5)
Irinotecan(n=0,0,3,3)	99999 (99999 to 99999)	99999 (99999 to 99999)	5.140 (5.1 to 9.61)	4.430 (3.95 to 5.08)
Metabolite SN-38(n=0,0,3,2)	99999 (99999 to 99999)	99999 (99999 to 99999)	12.000 (9.9 to 13.9)	10.390 (9.68 to 11.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1, Total Clearance (CL) of Eribulin and Irinotecan

End point title	Phase 1, Total Clearance (CL) of Eribulin and Irinotecan[7]

End point description:

Pharmacokinetic analysis set included subjects who had documented dosing history and at least one post-dosing quantifiable drug concentration. Here 'N' (overall number of subjects analyzed) included all subjects who were evaluable for this outcome measure and 'n' (number analyzed) included all subjects who were evaluable for each category. Here '99999' signifies that no subject was analyzed.

End point type	Secondary

End point timeframe:

For eribulin, Cycle 1 Day 1: 0-120 hours post-eribulin infusion; For irinotecan, Cycle 1 Day 1: 0-24 hours post-irinotecan infusion (cycle length=21 days)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was assessed in Phase 1 only.

End point values	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	2
Units: liter per hour (L/h)				
geometric mean (geometric coefficient of variation)				
Eribulin(n=3,3,3,2)	3.1781 (± 43.9)	2.4581 (± 8.0)	2.9060 (± 32.8)	1.7521 (± 136.6)
Irinotecan(n=0,0,3,3)	99999 (± 99999)	99999 (± 99999)	27.27 (± 23.2)	30.30 (± 60.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1, Volume of Distribution (Vz) of Eribulin and Irinotecan

End point title	Phase 1, Volume of Distribution (Vz) of Eribulin and

End point description:

Pharmacokinetic analysis set included subjects who had documented dosing history and at least one post-dosing quantifiable drug concentration. Here 'N' (overall number of subjects analyzed) included all subjects who were evaluable for this outcome measure and 'n' (number analyzed) included all subjects who were evaluable for each category. Here '99999' signifies that no subject was analyzed.

End point type	Secondary

End point timeframe:

For eribulin, Cycle 1 Day 1: 0-120 hours post-eribulin infusion; For irinotecan, Cycle 1 Day 1: 0-24 hours post-irinotecan infusion (cycle length=21 days)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was assessed in Phase 1 only.

End point values	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	2
Units: liter				
geometric mean (geometric coefficient of variation)				
Eribulin(n=3,3,3,2)	124.70 (± 41.5)	126.96 (± 18.1)	130.78 (± 35.9)	63.35 (± 101.8)
Irinotecan(n=0,0,3,3)	99999 (± 99999)	99999 (± 99999)	248.5 (± 16.1)	195.1 (± 69.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1, AUC(0-t): Area Under the Concentration-time Curve From Zero (Pre-dose) to Time of Last Quantifiable Concentration of of Eribulin, Irinotecan and its Active Metabolite SN-38

End point title	Phase 1, AUC(0-t): Area Under the Concentration-time Curve From Zero (Pre-dose) to Time of Last Quantifiable Concentration of of Eribulin, Irinotecan and its Active Metabolite SN-38[9]

End point description:

Pharmacokinetic analysis set included subjects who had documented dosing history and at least one post-dosing quantifiable drug concentration.

End point type	Secondary

End point timeframe:

For eribulin, Cycle 1 Day 1: 0-120 hours post-eribulin infusion; For irinotecan and its metabolite, Cycle 1 Day 1: 0-24 hours post-irinotecan infusion (cycle length=21 days)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was assessed in Phase 1 only.

End point values	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	3	3

Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
Eribulin	422.5 (± 40.0)	403.7 (± 32.1)	616.9 (± 66.1)	603.5 (± 87.3)
Irinotecan	1812.6 (± 13.5)	3686.1 (± 36.4)	4693.9 (± 66.1)	3633.7 (± 38.9)
Metabolite SN-38	68.00 (± 19.7)	145.04 (± 11.6)	138.22 (± 42.2)	65.47 (± 153.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1, AUC(0-inf): Area Under the Concentration-time Curve From Zero (Pre-dose) Extrapolated to Infinite Time of Eribulin, Irinotecan and its Active Metabolite SN-38

End point title	Phase 1, AUC(0-inf): Area Under the Concentration-time Curve From Zero (Pre-dose) Extrapolated to Infinite Time of Eribulin, Irinotecan and its Active Metabolite SN-38[10]

End point description:

Pharmacokinetic analysis set included subjects who had documented dosing history and at least one post-dosing quantifiable drug concentration. Here 'N' (overall number of subjects analyzed) included all subjects who were evaluable for this outcome measure and 'n' (number analyzed) included all subjects who were evaluable at specified timepoints for this outcome measure. Here '99999' signifies that no subject was analyzed.

End point type	Secondary

End point timeframe:

For eribulin, Cycle 1 Day 1: 0-120 hours post-eribulin infusion; For irinotecan and its metabolite, Cycle 1 Day 1: 0-24 hours post-irinotecan infusion (cycle length=21 days)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was assessed in Phase 1 only.

End point values	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	3	2
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				
Eribulin(n=3,3,3,2)	438.1 (± 39.0)	506.0 (± 16.6)	666.9 (± 69.0)	576.9 (± 133.6)
Irinotecan(0,0,3,3)	99999 (± 99999)	99999 (± 99999)	5036.1 (± 70.9)	3698.5 (± 39.2)
Metabolite SN-38(0,0,2,2)	99999 (± 99999)	99999 (± 99999)	169.0 (± 51.4)	149.4 (± 4.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression Free Survival (PFS)

End point title	Phase 2: Progression Free Survival (PFS)[11]

End point description:

PFS was defined as the time from date of first dose to the date of disease progression (PD) as determined by investigator assessment or death. PFS was assessed based on the investigators' assessments utilizing RECIST 1.1. PD was defined as at least a 20% increase or 5 mm increase in the sum of diameters of target lesions (taking as reference the smallest sum on study) recorded since the treatment started or the appearance of 1 or more new lesions. PFS was estimated and analyzed using Kaplan-Meier method. Full analysis set included subjects who received at least 1 dose of either study drug.

End point type	Secondary

End point timeframe:

From the date of first dose to the date of first documentation of PD, or date of death, whichever occurred first up to approximately 3 years 3 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was assessed in Phase 2 only.

End point values	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	9	
Units: months				
median (confidence interval 90%)	2.69 (1.28 to 8.87)	1.35 (1.15 to 2.79)	6.70 (1.38 to 8.84)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Clinical Benefit Rate (CBR)

End point title	Phase 2: Clinical Benefit Rate (CBR)[12]

End point description:

CBR was defined as the percentage of subjects with best overall response (BOR) of CR, PR, or durable stable disease (SD) based on RECIST 1.1 (durable SD was defined as SD with duration of greater than [>] 11 weeks). CR was disappearance of all target and non-target lesions. All pathological (whether target or non-target) must have a reduction in their short axis <10 mm. PR was at least a 30% decrease in the SOD of target lesions, taking as reference the baseline sum diameters. Full analysis set included subjects who received at least 1 dose of either study drug. Here 'N' (overall number of subjects analyzed) included all subjects who had CR, PR or SD.

End point type	Secondary

End point timeframe:

From the date of first dose to the date of first documentation of PD, or date of death, whichever occurred first up to approximately 3 years 3 months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was assessed in Phase 2 only.

End point values	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	3	5	
Units: percentage of subject				
number (confidence interval 90%)	55.6 (25.1 to 83.1)	33.3 (9.8 to 65.5)	55.6 (25.1 to 83.1)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after last dose of study drug (approximately 3 years 3 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2 intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 20 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Reporting group title	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Reporting group title	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2 and irinotecan hydrochloride 100 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Reporting group title	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m^2 and irinotecan hydrochloride 125 mg/m^2 intravenous infusion on Days 1 and 8 in a 21 day treatment cycle until MTD was reached. The MTD was determined based on the incidence of DLTs in cycle 1.

Reporting group title	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2

Reporting group description:

Subjects with RMS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Reporting group title	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2

Reporting group description:

Subjects with NRSTS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Reporting group title	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2

Reporting group description:

Subjects with EWS received eribulin mesylate 1.4 mg/m^2, intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m^2, intravenous infusion on Days 1 to 5 in a 21 day treatment cycle until disease progression, development of unacceptable toxicity or withdrawal of consent (approximately 39 months).

Serious adverse events	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	3 / 4 (75.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 4 (50.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	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 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (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	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (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			
Pain in jaw			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (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
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (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
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (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			
Malnutrition			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (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

Serious adverse events	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2
Total subjects affected by serious			

adverse events			
subjects affected / exposed	1 / 3 (33.33%)	5 / 9 (55.56%)	4 / 9 (44.44%)
number of deaths (all causes)	1	3	2
number of deaths resulting from adverse events	1	3	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 3 (33.33%)	1 / 9 (11.11%)	2 / 9 (22.22%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Malignant pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (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 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
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			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (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
Musculoskeletal and connective tissue disorders			

Pain in jaw			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (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
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (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
Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (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
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (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
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
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	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Malignant neoplasm progression			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant pleural effusion			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 9 (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	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in jaw			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Bacteraemia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Malnutrition				
subjects affected / exposed	0 / 9 (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: 0 %

Non-serious adverse events	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m^2	Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m^2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	4 / 4 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tumour pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Catheter site pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Catheter site pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Hypoxia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Respiratory distress			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Allergic cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Laryngeal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pneumothorax			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Agitation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Negative thoughts			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tearfulness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
C-reactive protein increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Neutrophil count decreased			

subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	0 / 3 (0.00%)
occurrences (all)	0	8	0
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 4 (75.00%)	0 / 3 (0.00%)
occurrences (all)	0	7	0
Blood albumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood calcium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood sodium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haematocrit decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Metamyelocyte count increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Myelocyte count increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Red blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Procedural nausea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Urostomy complication			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Mouth injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Wound dehiscence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1

Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 3 (66.67%)	2 / 4 (50.00%)	1 / 3 (33.33%)
occurrences (all)	3	14	6
Leukopenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	2 / 3 (66.67%)
occurrences (all)	4	14	15
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	3 / 3 (100.00%)	2 / 4 (50.00%)	3 / 3 (100.00%)
occurrences (all)	39	8	18
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	3
Leukocytosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	2 / 3 (66.67%)
occurrences (all)	1	0	2
Constipation			
subjects affected / exposed	2 / 3 (66.67%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	12	0
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	1 / 4 (25.00%)	2 / 3 (66.67%)
occurrences (all)	2	1	2
Oral pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	2 / 4 (50.00%)	3 / 3 (100.00%)
occurrences (all)	0	2	10
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Anal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Anal fissure			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haematemesis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Proctalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tongue ulceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Dermatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Skin oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Leukonychia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Papule			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary tract pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain in jaw			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rhinitis			

subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Tonsillitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular device infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Bacterial infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			

subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	2
Vitamin D deficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Refeeding syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m^2	Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2	Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m^2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	9 / 9 (100.00%)	9 / 9 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			

subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Tumour pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 9 (22.22%)	3 / 9 (33.33%)
occurrences (all)	0	2	3
Catheter site pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	2 / 9 (22.22%)
occurrences (all)	0	1	3
Catheter site pruritus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	2 / 9 (22.22%)	3 / 9 (33.33%)
occurrences (all)	0	5	3
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	2
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 3 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Hypoxia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Pleuritic pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory distress			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Allergic cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 9 (22.22%)	1 / 9 (11.11%)
occurrences (all)	0	2	2
Haemoptysis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Laryngeal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Pneumothorax			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Agitation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	8	0
Negative thoughts			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Tearfulness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	4	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	10	2
C-reactive protein increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	8	0
Weight decreased			

subjects affected / exposed	0 / 3 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Neutrophil count decreased			
subjects affected / exposed	2 / 3 (66.67%)	6 / 9 (66.67%)	3 / 9 (33.33%)
occurrences (all)	7	21	22
White blood cell count decreased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	1	20	6
Blood albumin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood calcium decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood potassium decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood sodium decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Blood urea increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0

Haematocrit decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	7	0
Metamyelocyte count increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Myelocyte count increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Red blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	5	0
Injury, poisoning and procedural complications			
Procedural nausea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Urostomy complication			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Mouth injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Wound dehiscence			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 3 (33.33%)	4 / 9 (44.44%)	0 / 9 (0.00%)
occurrences (all)	1	6	0
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	4
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 9 (33.33%)	4 / 9 (44.44%)
occurrences (all)	1	9	8
Leukopenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	12	0	1
Lymphopenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	3 / 9 (33.33%)	2 / 9 (22.22%)
occurrences (all)	12	15	10
Thrombocytopenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Leukocytosis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	7 / 9 (77.78%)	2 / 9 (22.22%)
occurrences (all)	0	9	3
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	4 / 9 (44.44%)	5 / 9 (55.56%)
occurrences (all)	0	24	11
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	4 / 9 (44.44%)	6 / 9 (66.67%)
occurrences (all)	0	5	8
Oral pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	6 / 9 (66.67%)	2 / 9 (22.22%)
occurrences (all)	3	8	2
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Anal inflammation			

subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Anal fissure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Aphthous ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gingival pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Haematemesis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Haematochezia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	4	0
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	4	1
Odynophagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Proctalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	5	0
Tongue ulceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	1	3	0
Dermatitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin oedema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 3 (33.33%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Leukonychia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Papule			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Urinary tract pain			

subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	2 / 9 (22.22%)
occurrences (all)	0	1	4
Bone pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Spinal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	2 / 9 (22.22%)
occurrences (all)	0	2	5
Groin pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	2 / 9 (22.22%)
occurrences (all)	0	1	3
Pain in jaw			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	4	0
Neck pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Conjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	3 / 9 (33.33%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Tonsillitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Vascular device infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Bacterial infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Device related infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0

Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	4 / 9 (44.44%)	3 / 9 (33.33%)
occurrences (all)	0	5	3
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 9 (22.22%)	0 / 9 (0.00%)
occurrences (all)	0	7	0
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Refeeding syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Non-serious adverse events	Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m^2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tumour pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Catheter site pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	8		
Catheter site pruritus			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Gait disturbance			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal			

disorders				
Cough				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Hypoxia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Pleuritic pain				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Respiratory distress				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Allergic cough				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Dyspnoea				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Epistaxis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Haemoptysis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Laryngeal inflammation				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Oropharyngeal pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Pneumothorax				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Pulmonary embolism				

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Agitation			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Depressed mood			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Negative thoughts			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Tearfulness			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	5		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	9		
C-reactive protein increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			

subjects affected / exposed	2 / 9 (22.22%)			
occurrences (all)	5			
Weight decreased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Neutrophil count decreased				
subjects affected / exposed	5 / 9 (55.56%)			
occurrences (all)	46			
White blood cell count decreased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Blood albumin decreased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Blood calcium decreased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Blood creatinine increased				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Blood phosphorus decreased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Blood potassium decreased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Blood sodium decreased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Blood urea increased				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	2			
Gamma-glutamyltransferase				

increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Haematocrit decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Metamyelocyte count increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Myelocyte count increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Red blood cell count decreased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Procedural nausea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Urostomy complication			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Mouth injury			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Wound dehiscence			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Cardiac disorders			

Tachycardia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Neuralgia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	29		
Leukopenia			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	32		
Lymphopenia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	52		
Thrombocytopenia			

subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	17		
Leukocytosis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Oral pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Abdominal distension			

subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Anal inflammation				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Anal fissure				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Aphthous ulcer				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Gingival pain				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Haematemesis				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Haematochezia				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Hypoaesthesia oral				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Mouth ulceration				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	1			
Odynophagia				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	1			
Proctalgia				
subjects affected / exposed	0 / 9 (0.00%)			
occurrences (all)	0			
Stomatitis				
subjects affected / exposed	1 / 9 (11.11%)			
occurrences (all)	4			
Tongue ulceration				

subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Dermatitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Skin oedema			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Leukonychia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Papule			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Haematuria			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		
Urinary tract pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Spinal pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Arthralgia			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	5		
Groin pain			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Pain in jaw			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	3		
Neck pain			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Tonsillitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Vascular device infection			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Bacterial infection			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
COVID-19			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Device related infection			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Ear infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Herpes simplex			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

Pneumonia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Hypophosphataemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 3		
Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 10		
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Refeeding syndrome subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2018	Amendment 01: Up to approximately 50 study sites was added. Ewing sarcoma (EWS) as a treatment group was added. Included duration of response (DOR) as part of the primary objective for Phase 2. Expanded maximum number of subjects for Phase 2 of study from 50 to 75, consistent with addition of an EWS treatment group. Subjects <12 months are included for descriptive purposes only and will not contribute to the determination of the MTD/RP2D for this study, or to the sample size. Eligibility criteria was amended. PK sampling schedule for subjects <12 months was included. Updated Principles of the World Medical Association Declaration of Helsinki from 2008 to 2013. Included storage and labeling information for irinotecan hydrochloride as an Investigational Product. schedule of assessments was amended.
02 August 2018	Amendment 02: Added restriction to concomitant use with St. John's Wort in exclusion criterion #2. Added criteria for study drug discontinuation. Added new Tables (Tables 3 and 8) which list the criteria for study drug discontinuation. Amended PK sampling schedule to reduce the frequency of PK blood draws in relation to the subjects weight/blood volume. Subjects under 6 kg will not have samples for PK analysis taken.
12 October 2018	Amendment 03: Updated the exploratory objective 'To explore the relationship between model-derived exposure to eribulin and the active metabolite for irinotecan (SN 38) in terms of area under the curve and AEs and efficacy endpoints using a model-based approach'. Clarification that the duration of treatment up to 1 year is from the 'start of study treatment'. ECG and electrolyte monitoring will occur 'more frequently in consultation with cardiologist advice and in line with local practice'. For neuroblastoma subjects (Phase 1 only), included MIBG assessments and when to perform them. Updated interim analyses to include an assessment of tolerability. Removed 'safety summaries may be provided periodically' due to this update. Included monthly pregnancy tests are required for all sexually active subjects. Removed assessment for globulin. Updated sponsor's grading for CTCAE laboratory values.
10 July 2019	Amendment 04: Updated description of sample size for Phase 2 to 'approximately 75' or 'approximately 25 per histology' and updated trial schema. Updated inclusion criterion #8 to remove the use of radioisotope for the measurement of the glomerular filtration rate (GFR). Amended exclusion criterion #3 to allow subjects who received prior therapy with irinotecan hydrochloride in Phase 2 if there was no tumor progression during prior irinotecan therapy. Updated exclusion criterion #9. Added FDG-PET scans. Updated details of MIBG scans for neuroblastoma patients. Updated the description of safety data analysis in statistical methods section. Updated estimated study LSLV date (to Mar 2021). Updated description of laboratory analysis values, ECG and other safety analyses. Minor administrative changes.

14 July 2020	Amendment 05: Extended study duration from 36 to 42 months. As per protocol amendment #5, the recommended Phase 2 dose (RP2D) was selected to be Schedule A Dose Level 1 – eribulin (1.4 mg/m2) Day 1 and Day 8 and irinotecan (40 mg/m2) Days 1-5. Updated Inclusion Criterion 1a. Updated Exclusion Criterion 10. Criteria for administration of study drug; Day 8 Bowel function deteriorated since pretreatment/ baseline and requires antidiarrheal medications for within 24 hours before the next administration of irinotecan hydrochloride. Included dose levels specifically for the Phase 2 portion of the study. For bone scans, added: approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated. Bone lesions must be followed with anatomic imaging. Included 'irrespective of dose delays' In instances where a subject becomes pregnant, the following language has been included "The Investigator should confirm whether they agree to follow-up assessments (including survival follow-up) or whether the subject wishes to withdraw consent. If a subject withdraws consent, the date should be documented in the source documents".
29 March 2021	Amendment 06: To clarify subjects aged >6 months and <12 months will be enrolled to Schedule A with a modified dose of eribulin Dose Level -2 (0.8 mg/m2 Day 1 and Day 8) with the irinotecan dose maintained Dose Level 1 (40 mg/m2 Day 1 – Day 5) of a 21-day cycle. Amended Inclusion Criterion 1b to include subjects >6 months and <12 months of age in Phase 2. For subjects >6 months and <12 months of age in Phase 2, further dose reductions have been included for this age group for eribulin in case of toxicities requiring a dose reduction. Specified if toxicities do not recover after 2 dose reductions, treatment with that agent must be discontinued. Pharmacokinetic (PK): Specified that subjects who weigh under 6 kg will not have samples for PK analysis taken. Vital signs, physical examination, and chemistry assessments during Phase 2 for the >6 months and <12 months age group will be weekly. Subjects in the age groups > 6 months to < 12 months and ≥18 to ≤25 years old are included for descriptive purposes only and will not contribute to the full sample size analyses. Subjects in the age group > 6 months to <12 months will receive approximately 75% of the RP2D of eribulin (rationale for lower dose is provided in Section 9.4.4) and therefore should not been included in the full sample size analyses. The EMA PDCO requested that subjects in the age group ≥18 to ≤25 years old should not be included in the full sample size analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 April 2020	New screening or enrollment was temporarily halted on all sites on study for the period of 01 Apr 2020 to 30 Apr 2020 to reduce the risk of potential COVID-19 exposure.	-

Notes:

Limitations and caveats

None reported