



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 | v2 (current) |
| This version publication date | 09 August 2022 |
| First version publication date | 02 December 2021 |
| Version creation reason | |

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) | EMA-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 informed 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/m²) intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 20 mg/m², 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/m², 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/m², 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/m², intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m², 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/m², 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/m², 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/m² and irinotecan hydrochloride 100 mg/m² 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/m² 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/m² 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/m² and irinotecan hydrochloride 125 mg/m² 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/m² 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/m² 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/m², intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m², 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/m², 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/m², 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/m², intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m², 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/m², 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/m², 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/m², intravenous infusion on Days 1 and 8 and Irinotecan hydrochloride 40 mg/m², 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/m², 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/m², 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+Iri- notecan 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/m² intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 20 mg/m², 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/m² and irinotecan hydrochloride 100 mg/m² 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: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m ² |
|-----------------------|--|

Reporting group description:

Subjects with EWS received eribulin mesylate 1.4 mg/m², intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m², 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: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m ² |
|-----------------------|--|

Reporting group description:

Subjects with RMS received eribulin mesylate 1.4 mg/m², intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m², 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/m², intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m², 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 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m ² |
|-----------------------|--|

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m², intravenous infusion on Days 1 and 8 and irinotecan hydrochloride 40 mg/m², 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 125 mg/m ² |
|-----------------------|---|

Reporting group description:

Subjects received eribulin mesylate 1.4 mg/m² and irinotecan hydrochloride 125 mg/m² 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.

| Serious adverse events | Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 20 mg/m ² | Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 100 mg/m ² | Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m ² |
|---|--|---|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 3 / 9 (33.33%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (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 |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (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 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 9 (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 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (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%) | 0 / 3 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|--|--|--|
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 9 (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 / 3 (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 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (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 |
| Metabolism and nutrition disorders | | | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (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 |
| Serious adverse events | Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m ² | Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m ² | Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m ² |

| | | | |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 9 (55.56%) | 4 / 9 (44.44%) | 3 / 4 (75.00%) |
| number of deaths (all causes) | 3 | 2 | 1 |
| number of deaths resulting from adverse events | 3 | 2 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 2 / 9 (22.22%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 2 / 4 (50.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|----------------|----------------|---------------|
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (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 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (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 | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (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 | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (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 |

| | | | |
|---|---|--|--|
| Serious adverse events | Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m ² | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|---|----------------|--|--|
| Malignant neoplasm progression subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Malignant pleural effusion subjects affected / exposed | 0 / 3 (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 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed | 0 / 3 (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 / 3 (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 | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |

| | | | |
|---|---------------|--|--|
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 3 (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 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (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 / 3 (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 B, Eribulin Mesylate + Irinotecan 100 mg/m ² | Phase 2: EWS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m ² |
|---|--|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 3 / 3 (100.00%) | 9 / 9 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tumour pain | | | |

| | | | |
|---|--------------------|--------------------|--------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Catheter site pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 5 / 9 (55.56%) |
| occurrences (all) | 1 | 1 | 8 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 1 | 2 |
| Catheter site pruritus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 9 (22.22%) |
| occurrences (all) | 0 | 0 | 4 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 1 | 1 |
| Hypoxia | | | |

| | | | |
|-----------------------------|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Allergic cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Laryngeal inflammation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |

| | | | |
|--------------------------------------|---------------|----------------|----------------|
| Insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Agitation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Negative thoughts | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tearfulness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 2 / 9 (22.22%) |
| occurrences (all) | 0 | 2 | 9 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 5 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 9 (22.22%) |
| occurrences (all) | 0 | 0 | 5 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 5 / 9 (55.56%) |
| occurrences (all) | 0 | 0 | 46 |
| Weight decreased | | | |

| | | | |
|-------------------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 1 | 1 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood calcium decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 2 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Haematocrit decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|---------------------|--------------------|---------------------|
| Metamyelocyte count increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Myelocyte count increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Red blood cell count decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural nausea subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Urostomy complication subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Contusion subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Fall subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Mouth injury subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Wound dehiscence subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Cardiac disorders | | | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Nervous system disorders | | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |

| | | | |
|--------------------------------------|-----------------|-----------------|----------------|
| Headache | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 1 | 2 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Peripheral sensorimotor neuropathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 3 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Syncope | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 1 / 3 (33.33%) | 5 / 9 (55.56%) |
| occurrences (all) | 3 | 6 | 29 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 3 / 9 (33.33%) |
| occurrences (all) | 4 | 15 | 32 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 3 / 3 (100.00%) | 4 / 9 (44.44%) |
| occurrences (all) | 39 | 18 | 52 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 5 / 9 (55.56%) |
| occurrences (all) | 0 | 3 | 17 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| Ear pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 2 / 9 (22.22%) |
| occurrences (all) | 1 | 0 | 2 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Constipation | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 0 / 3 (0.00%) | 2 / 9 (22.22%) |
| occurrences (all) | 3 | 0 | 2 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 5 / 9 (55.56%) |
| occurrences (all) | 1 | 0 | 9 |
| Nausea | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 1 / 9 (11.11%) |
| occurrences (all) | 2 | 2 | 1 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 3 (100.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 10 | 4 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Anal inflammation | | | |

| | | | |
|--|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 4 |
| Tongue ulceration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|----------------|----------------|----------------|
| Dermatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukonychia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 9 (22.22%) |
| occurrences (all) | 0 | 0 | 2 |
| Papule | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (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 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 3 |
| Urinary tract pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |

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

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 1 | 2 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory tract infection | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 1 / 3 (33.33%) 2 | 1 / 9 (11.11%) 3 |
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 3 (33.33%) 1 | 0 / 9 (0.00%) 0 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 2 / 9 (22.22%) 10 |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Refeeding syndrome subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 3 (0.00%) 0 | 0 / 9 (0.00%) 0 |

| Non-serious adverse events | Phase 2: RMS Cohort, Eribulin Mesylate + Irinotecan 40 mg/m ² | Phase 2: NRSTS Cohort, Eribulin Mesylate+Irinotecan 40 mg/m ² | Phase 1: Schedule A, Eribulin Mesylate + Irinotecan 40 mg/m ² |
|---|--|---|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 9 / 9 (100.00%) | 9 / 9 (100.00%) | 4 / 4 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Cancer pain | | | |

| | | | |
|--|----------------|----------------|---------------|
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 3 / 9 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 2 / 9 (22.22%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site pruritus | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 3 / 9 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 5 | 3 | 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Cough | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Allergic cough | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Laryngeal inflammation | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|----------------------|---------------------|---------------------|
| Rhinorrhoea subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 1 / 9 (11.11%) 1 | 1 / 4 (25.00%) 3 |
| Agitation subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 4 (0.00%) 0 |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Depressed mood subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 8 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Negative thoughts subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Tearfulness subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 3 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 10 | 1 / 9 (11.11%) 2 | 0 / 4 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 4 | 0 / 9 (0.00%) 0 | 1 / 4 (25.00%) 2 |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 8 | 0 / 9 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Neutrophil count decreased | | | |

| | | | |
|-------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 6 / 9 (66.67%) | 3 / 9 (33.33%) | 3 / 4 (75.00%) |
| occurrences (all) | 21 | 22 | 8 |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 0 / 9 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 2 | 0 | 1 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 9 (11.11%) | 3 / 4 (75.00%) |
| occurrences (all) | 20 | 6 | 7 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood calcium decreased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Haematocrit decreased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 7 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Metamyelocyte count increased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Myelocyte count increased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Red blood cell count decreased subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 5 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Procedural nausea subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Urostomy complication subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 4 (25.00%) 1 |
| Contusion subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Fall subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Mouth injury subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Wound dehiscence subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 2 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Cardiac disorders | | | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 9 (0.00%) 0 | 2 / 9 (22.22%) 2 | 0 / 4 (0.00%) 0 |
| Nervous system disorders | | | |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Headache | | | |
| subjects affected / exposed | 4 / 9 (44.44%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peripheral sensorimotor neuropathy | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | 4 / 9 (44.44%) | 2 / 4 (50.00%) |
| occurrences (all) | 9 | 8 | 14 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 14 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | 2 / 9 (22.22%) | 2 / 4 (50.00%) |
| occurrences (all) | 15 | 10 | 8 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Leukocytosis | | | |

| | | | |
|--|---------------------|--------------------|--------------------|
| subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | 0 / 9 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 7 / 9 (77.78%) | 2 / 9 (22.22%) | 0 / 4 (0.00%) |
| occurrences (all) | 9 | 3 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 9 (44.44%) | 5 / 9 (55.56%) | 1 / 4 (25.00%) |
| occurrences (all) | 24 | 11 | 12 |
| Nausea | | | |
| subjects affected / exposed | 4 / 9 (44.44%) | 6 / 9 (66.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 5 | 8 | 1 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 6 / 9 (66.67%) | 2 / 9 (22.22%) | 2 / 4 (50.00%) |
| occurrences (all) | 8 | 2 | 2 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Anal fissure | | | |

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

| | | | |
|---|----------------|----------------|---------------|
| Alopecia | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin oedema | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukonychia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Papule | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Urinary tract pain | | | |

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

| | | | |
|-----------------------------|----------------|----------------|----------------|
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 3 / 9 (33.33%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|----------------|----------------|
| Pneumonia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 9 (44.44%) | 3 / 9 (33.33%) | 1 / 4 (25.00%) |
| occurrences (all) | 5 | 3 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 9 (22.22%) | 0 / 9 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Refeeding syndrome | | | |
| subjects affected / exposed | 0 / 9 (0.00%) | 1 / 9 (11.11%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Non-serious adverse events | Phase 1: Schedule B, Eribulin Mesylate + Irinotecan 125 mg/m ² | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | | |

| | | | |
|---|---------------|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Catheter site pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Catheter site pruritus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal | | | |

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

| | | | |
|--------------------------------------|---------------|--|--|
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Negative thoughts | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tearfulness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lymphocyte count decreased | | | |

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

| | | | |
|--|---------------|--|--|
| increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haematocrit decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metamyelocyte count increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myelocyte count increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Red blood cell count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Procedural nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urostomy complication | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fall | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mouth injury | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |

| | | | |
|--|----------------------|--|--|
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | | |
| Nervous system disorders | | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | | |
| Headache subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | | |
| Neuralgia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | | |
| Peripheral sensorimotor neuropathy subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | | |
| Syncope subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | | |
| Leukopenia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 12 | | |
| Lymphopenia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 3 | | |
| Neutropenia subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 12 | | |
| Thrombocytopenia | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Toothache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 3 | | |
| Abdominal distension | | | |

| | | | |
|-----------------------------|---------------|--|--|
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anal inflammation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gingival pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tongue ulceration | | | |

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

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

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|------------------------------------|---------------|--|--|
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Refeeding syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 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. |

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|---------------|--|
| 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/m ²) Day 1 and Day 8 and irinotecan (40 mg/m ²) 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/m ² Day 1 and Day 8) with the irinotecan dose maintained Dose Level 1 (40 mg/m ² 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