London, 29 May 2019
EMA/335387/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Halaven

eribulin

Procedure no: EMEA/H/C/002084/P46/023

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 14 March 2019, the MAH submitted a completed paediatric study for Halaven, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

No changes to the eribulin Summary of Product Characteristics (SmPC) derive from the data of this study.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the phase 1 study of Eribulin mesylate, a Novel Microtubule targeting Chemotherapeutic Agent in Children with Refractory or recurrent Solid Tumors (Excluding CNS), Including Lymphomas, Study No. E7389-A001-113 is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

Eribulin mesylate was administered either directly as an IV injection over 2 to 5 minutes or diluted in up to 100 mL 0.9% saline for IV infusion over 15 minutes on Days 1 and 8 of each 21-day cycle. Eribulin mesylate was supplied in 2-mL single-use vials. The following batch number was used in the study: N1200923 (expiry 25 Oct 2017).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- Study No. E7389-A001-113 A Phase 1 Study of Eribulin Mesylate, a Novel Microtubule Targeting Chemotherapeutic Agent in Children with Refractory or Recurrent Solid Tumors (Excluding CNS), Including Lymphomas

2.3.2. Clinical study

Study E7389-A001-113

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

Methods

Study design

This was a Phase 1, open-label, dose escalation study of eribulin mesylate given intravenously on Days 1 and 8 of a 21-day cycle in pediatric subjects with recurrent or refractory solid tumors (excluding CNS), including lymphomas. The starting dose for the study was 1.1 mg/m^2 and dose escalation occurred according to the schema, see Dose escalation Table 1. The Day 8 dose could be delayed or omitted in the event of toxicities.

Eligible subjects were enrolled into either Part A1 or A2 of the study based on age. Subjects ≥12 months and <18 years of age were eligible for enrolment in Part A1. Subjects >6 months but <12 months of age were eligible for enrolment in Part A2.

Study population

Key inclusion criteria are provided below:

1. Paediatric subjects (age > 6 months and < 18 years) were eligible to take part in the study if they had refractory or recurrent solid tumours (excluding CNS) or lymphomas with histologic verification of malignancy at original diagnosis or relapse.
2. Subjects were required to have measurable or evaluable disease to be eligible for entry into the study. Measurable disease was defined as the presence of at least 1 measurable lesion categorized at baseline as ≥10 mm in the longest diameter for a non-lymph node or ≥15 mm in the short-axis diameter for a lymph node as determined by the investigator using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1). Evaluable disease was defined as the presence of at least one lesion, with no lesion that could be accurately measured in at least one dimension.
3. Subjects must have been fully recovered from the acute toxic effects of all prior anticancer chemotherapy, have adequate bone marrow, renal, liver and cardiac function.
4. Performance status per the paediatric specific scales Lansky (≤16 years) and Karnofsky (>16 years) ≥50 was required at baseline.

Key exclusion criteria are provided below:

1. Concomitant Medications

- Corticosteroids: Subjects receiving corticosteroids who were not on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrolment were not eligible.

- Investigational Drugs: Subjects who were receiving another investigational drug were not eligible.

- Anticancer Agents: Subjects who were receiving other anticancer agents were not eligible.

- Anti-GVHD agents post-transplant: Subjects who were receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post allogeneic bone marrow transplant were not eligible for this study.

- QTc agents: Subjects who were receiving drugs that prolong the QTc were not eligible (refer to Category 1 of Protocol, Appendix II for a list of agents)

2. Infection: Subjects who had a prior history of viral hepatitis (B or C) as demonstrated by positive serology (presence of antigens) or had an uncontrolled infection requiring treatment were not eligible.

3. Subjects with > Grade 1 peripheral sensory neuropathy or > Grade 1 peripheral motor neuropathy graded according to the Modified (“Balis”) Pediatric Scale of Peripheral Neuropathies were not eligible (see Protocol, Appendix III).

4. Cardiac Pathology: Subjects with known congestive heart failure, symptomatic or LV ejection fraction <50% or shortening fraction <27% were not eligible; subjects with congenital long QT syndrome, bradyarrhythmias, or QTc >480 msec were not eligible.

5. Central Nervous System (CNS) Disease: Subjects with primary CNS tumours were not eligible; Subjects with prior history of or known metastatic CNS disease involvement were not eligible. Note:

CNS imaging for subjects without a known history of CNS disease was only required if clinically indicated.

6. Surgery: Subjects who had had or were planning to have the following invasive procedures were not eligible:

- Major surgical procedure, laparoscopic procedure, open biopsy or significant traumatic injury within 28 days prior to enrolment.

- Central line placement or subcutaneous port placement was not considered major surgery but must have been placed at least 3 days prior to enrolment for external lines (eg, Hickman or Broviac) and at least 7 days prior to enrolment for subcutaneous port.

- Core biopsy within 7 days prior to enrolment.

- Fine needle aspirate within 7 days prior to enrolment.

NOTE: For purposes of this study, bone marrow aspirate and biopsy are not considered surgical procedures and therefore are permitted within 14 days prior to start of protocol therapy.

7. Subjects with known bone marrow involvement were not eligible.

8. Subjects who had received a prior solid organ transplantation were not eligible.

Assessor's comment

A Karnofsky (>16 years) or Lansky (≤ 16 years) performance score of ≥50 was required for inclusion. A Karnofsky score of 50 corresponds to an ECOG score of 3 (according to ESMO), thus patients with relatively poor performance were eligible. It is noted, however, that only two patients (2/22) with a score of 50 were recruited.

Treatments

During the Treatment Phase, eribulin mesylate was administered as an IV infusion over 2 to 5 minutes on Days 1 and 8 of each 21-day cycle. Eribulin mesylate could also be administered as an IV infusion over 15 minutes to allow younger subjects to receive a diluted infusion when clinically appropriate.

A cycle was repeated every 21 days if the subject had at least stable disease and still met laboratory parameters as defined in the eligibility section. Study assessments were to be performed within 72 hours prior to the start of the subsequent cycle.

Dose escalation

The dose escalation schema is presented in Table 1. The starting dose for the study was 1.1 mg/m^2 which is approximately 80% of the adult MTD. The study used a rolling 6 design for dose escalation. Up to 6 eligible subjects were concurrently enrolled on to a dose level, dependent on: 1) number of subjects enrolled at the current dose level; 2) number of subjects who had experienced a dose-limiting toxicity (DLT) at the current dose level; 3) number of subjects entered but with tolerability data pending at the current dose level. In order to maximize safety for infants in Part A2, they were to be enrolled in a separate stratum, at one dose level below that at which children ≥12 months of age were enrolling.

Table 1 Dosing escalation schema

Dose level	Dose of eribulin mesylate
-1	0.8 mg/m^2

1 (Starting dose)	**1.1 mg/m^2**
2	1.4 mg/m^2
3	1.8 mg/m^2
4	2.2 mg/m^2

The study consisted of 3 Phases: the Pretreatment Phase, the Treatment Phase and the Follow-up Phase. The Pretreatment Phase included assessments before the first dose of study drug to establish eligibility and baseline values. The Treatment Phase included a dose-escalation period. The starting dose was 1.1 mg/m^2 and the selection of subsequent dose levels was performed using the rolling 6 design until the MTD and/or recommended Phase 2 dose (RP2D) was determined. Dose-limiting toxicities (DLTs) were measured in Cycle 1 of each subject's initially assigned dose. Intra-subject dose escalation was not allowed. The MTD was defined as the maximum dose at which less than one third of subjects experienced a DLT during Cycle 1. Additional subjects were to be enrolled at the MTD for evaluation of PK (PK expansion Cohort). Toxicities occurring after Cycle 1 were also reviewed, but did not count as DLTs. If clinically relevant toxicities were observed at any dose level after Cycle 1, the dose was modified as described in the protocol. Toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Study treatment was discontinued if there was evidence of progressive disease (PD) or drug related DLT that required removal from treatment. Study treatment may otherwise continue provided the subject had at least stable disease, met laboratory parameters defined in the eligibility criteria and did not meet any of the criteria for removal from protocol therapy or off study criteria. Subjects were followed for 30 days from the last dose of eribulin mesylate to provide any additional information about on-going and long-term toxicities. The study was ended 30 days after the last dose was administered to the last subject.

This study was conducted by an external cooperative group, the Children's Oncology Group (COG). The COG developed the protocol and database for this study, and Eisai Inc. acted as Sponsor and performed the analysis.

Dose escalation/de-escalation decisions and determination of the MTD were made by the Study Chair (COG) DVL Statistician, DVL committee Chair or vice chair and the Sponsor based on the review of the safety and available PK data.

Please refer to the protocol for further information regarding Definition of Dose-Limiting Toxicity.

Pharmacokinetic sampling

Rich PK sampling was performed after the first dose of eribulin, at 10 (± 5) and 30 minutes, 1, 2, 4, 6, 24, 48, 72 and 96 or 120 hours. Pre-dose and post infusion samples were also taken at day 8. Pharmacokinetic analysis for eribulin mesylate in plasma was conducted by Eisai Inc. using a HPLC with MS/MS detection.

Endpoints

Primary endpoints

• MTD was determined by the appearance of DLTs following the treatment of eribulin mesylate given intravenously on Days 1 and 8 of Cycle 1. MTD was defined as thehighest dose at which less than 1/3 subjects experienced a DLT during Cycle 1. The number of DLTs during Cycle 1, for subjects who

completed both Day 1 and 8 doses, was the primary endpoint for this study. DLTs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE Version 4.0).

• The safety of eribulin mesylate was determined by analyzing the following endpoints:

- Incidence of AEs

- Values observed for clinical laboratory, EKG, and vital sign parameters

- Incidence of abnormal clinical laboratory, EKG, and vital sign results

• Pharmacokinetic endpoints:

- Terminal half-life (t½)

- Maximum concentration (Cmax)

- Time to maximum concentration (tmax)

- Area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration (AUC0-t)

- Area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time (AUC0-inf)

- Clearance (CL)

- Volume of Distribution (Vd)

Secondary endpoints

The secondary efficacy endpoints were tumor assessment and tumor response.

Sample size

Part A1: Subjects ≥12 months and <18 years of age

A minimum of 2 evaluable subjects were entered at each dose level for determination of MTD. Once the MTD or RP2D was defined, up to 6 additional subjects were enrolled on that dose to acquire PK data in a representative number of young subjects (ie, subjects ≥ 12 months and <12 years old).

Part A2: Subjects >6 months and <12 months of age

Subjects in Part A2 of the study enrolled one dose level behind the dose level at which subjects in Part A1 were enrolling. Part A2 was open to enrolment on Dose Level 1 once Part A1 had escalated to Dose Level 2. Up to 6 evaluable subjects were enrolled in each lagging dose level. If at any time 2 or more evaluable subjects at a lagging dose level experienced a DLT, Part A2 was to be closed to further accrual.

Review of the enrolment rate into previous COG new agent studies indicates that 1 to 2 subjects per month were available, which permitted completion of the study within 33 to 65 months In Part A1, a maximum of 65 subjects was anticipated which accounts for a 20% inevaluability rate for the Dose Evaluable Set (DES) and assuming that all 4 dose levels are studied and require expansion to 12 subjects. A maximum of 29 subjects was anticipated in Part A2, which accounts for a 20% inevaluability rate for the DES.

Statistical Methods

Analysis Sets: Safety analysis set (SAS) consisted of subjects who received at least one dose of study drug. Dose evaluable set (DES) consisted of subjects who were judged as DLT evaluable as recorded in the database. In order to be DLT evaluable, all subjects had to complete Cycle 1. DES was used for determination of MTD based on DLT assessments at each dose level for dose-escalation. Pharmacokinetic analysis set (PAS) consisted of subjects who had sufficient PK data to derive at least one PK parameter. PAS was the analysis set for PK analysis.

Efficacy Analysis: No formal statistical analysis was planned.

Assessor's comment

It is noted that no formal efficacy statistical analysis was planned.

Changes in the conduct of the study or planned analyses

There were 2 amendments to the original protocol, dated 30 Jun 2014.

Amendment #1 (Amendment 1A, dated 12 Feb 2015) was provided in response to a

Disapproval letter from the Cancer Therapy Evaluation Program (CTEP, dated 27 January 2015) who wanted further clarification on the management of subjects with Day 8 doselimiting neutropenia and administration of myeloid growth factor support. The amendment also contained revisions to update the schedule for the PK studies and the Day 8 dose modification guidelines. Additional administrative changes were made for clarity and consistency.

Amendment #2 (Amendment 2, dated 29 Jun 2016) included additional administrative changes for clarity and consistency, and updates to the study committee contact information.

Assessor's comment

There were 2 amendments to the original protocol, dated 30 Jun 2014. Both amendments were considered not to affect the primary and secondary endpoints.

2.3.2.1. Results

Recruitment/ Number analysed

Study E7389-A001-113 was conducted in 18 centres in the United States from 31 Jul 2014.

A total of 23 subjects were enrolled in the study and, of these, 22 subjects received study treatment at doses between 1.1 and 1.8 mg/m^2. One subject was withdrawn from the study due to progressive disease prior to receiving any study treatment.

Of the 22 subjects enrolled and treated in the study, the majority of subjects (81.8%) discontinued study treatment due to progressive disease. One subject in the PK expansion cohort died while on treatment due to a TEAE of hypoxia.

Assessor's comment

The first subject was enrolled 31 July 2014 and the last subject's last visit was 28 January 2016.

Data sets analysed

A total of 22 subjects received at least one dose of study drug and were included in the SAS and PK Analysis Set. Twenty subjects were judged as DLT evaluable and were included in the DES.

Following Study Chair review of the SAS, 2 subjects were excluded from the DES:

• came off protocol therapy prior to Day 8 and had no DLT during Cycle 1.

• received all required therapy in Cycle 1, but did not have all the required laboratory observations due to progressive disease.

Table 2 Summary of analysis sets – Part A1 (all subjects)

	Dose escalation			PK expansion	Combined	
	1.1 mg/m² (N=6) n (%)	**1.4 mg/m² (N=6) n (%)**	**1.8 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=6) n (%)**	**1.4 mg/m² (N=12) n (%)**	**Total (N=23) n (%)**
Safety analysis set	6 (100.0)	6 (100.0)	5 (100.0)	5 (83.3)	11 (91.7)	22 (95.7)
Dose evaluable set	6 (100.0)	6 (100.0)	5 (100.0)	3 (50.0)	9 (75.0)	20 (87.0)
PK analysis set	6 (100.0)	6 (100.0)	5 (100.0)	5 (83.3)	11 (91.7)	22 (95.7)

Assessor's comment

A total of 23 subjects were enrolled in the study and 22 were treated with at least one dose of eribulin (Part A1). One subject was withdrawn from the study due to progressive disease prior to receiving any study treatment.

It is noted that there were no subjects (>6 months but <12 months of age) included in Part A2.

Baseline data

Table 3 Demography and Baseline Characteristics – Part A1 (Safety Analysis Set)

	Dose Escalation			**PK Expansion**	**Combined**	
	1.1 mg/m² (N=6)	**1.4 mg/m² (N=6)**	**1.8 mg/m² (N=5)**	**1.4 mg/m² (N=5)**	**1.4 mg/m² (N=11)**	**Total (N=22)**
Age(year)	**n=6**	**n=6**	**n=5**	**n=5**	**n=11**	**n=22**
Mean (SD)	14.0 (3.52)	10.7 (2.25)	13.0 (3.24)	12.6 (5.50)	11.5 (3.96)	12.5 (3.69)
Median (Min, Max)	15.5 (7, 16)	11.0 (8, 13)	13.0 (8, 17)	14.0 (3, 17)	13.0 (3, 17)	13.5 (3, 17)
Q1, Q3	14.0, 16.0	8.0, 13.0	13.0, 14.0	14.0, 15.0	8.0, 14.0	11.0, 15.0

Age Group, n (%)						
≥12 months to <2 years	0	0	0	0	0	0
≥2 years to <12 years	1 (16.7)	4 (66.7)	1 (20.0)	1 (20.0)	5 (45.5)	7 (31.8)
≥12 years to <18 years	5 (83.3)	2 (33.3)	4 (80.0)	4 (80.0)	6 (54.5)	15 (68.2)
Sex, n (%)						
Male	5 (83.3)	2 (33.3)	2 (40.0)	3 (60.0)	5 (45.5)	12 (54.5)
Female	1 (16.7)	4 (66.7)	3 (60.0)	2 (40.0)	6 (54.5)	10 (45.5)
Weight(kg)	**n=6**	**n=6**	**n=5**	**n=5**	**n=11**	**n=22**
Mean (SD)	60.02 (22.936)	36.85 (8.718)	54.18 (17.505)	49.36 (29.539)	42.54 (20.730)	49.95 (21.219)
Median (Min, Max)	60.75 (20.1, 87.1)	38.00 (22.3, 46.8)	55.70 (31.4, 77.2)	43.90 (13.2, 92.9)	42.00 (13.2, 92.9)	45.40 (13.2, 92.9)
Q1, Q3	54.80, 76.60	34.00, 42.00	44.00, 62.60	37.10, 59.70	34.00, 46.80	34.00, 61.10
Height(cm)	**n=6**	**n=6**	**n=5**	**n=5**	**n=11**	**n=22**
Mean (SD)	156.92 (19.956)	145.35 (12.837)	156.02 (11.619)	151.38 (36.963)	148.09 (25.275)	152.30 (21.057)
Median	162.00 (117.0, 170.0)	147.95 (128.2, 161.0)	156.70 (139.4, 172.0)	164.00 (89.0, 185.5)	151.20 (89.0, 185.5)	157.35 (89.0, 185.5)
Q1, Q3	161.00, 169.50	132.00, 155.00	154.00, 158.00	151.20, 167.20	132.00, 164.00	147.90, 164.00
BSA(m^2)	**n=6**	**n=6**	**n=5**	**n=5**	**n=11**	**n=22**
Mean (SD)	1.600 (0.4194)	1.213 (0.1940)	1.516 (0.2703)	1.418 (0.5931)	1.306 (0.4134)	1.434 (0.3940)
Median (Min, Max)	1.670 (0.81, 2.02)	1.255 (0.89, 1.45)	1.630 (1.11, 1.80)	1.410 (0.57, 2.19)	1.310 (0.57, 2.19)	1.430 (0.57, 2.19)
Q1, Q3	1.570, 1.860	1.120, 1.310	1.390, 1.650	1.250, 1.670	1.120, 1.450	1.200, 1.670
Race, n (%)						
White	5 (83.3)	5 (83.3)	4 (80.0)	2 (40.0)	7 (63.6)	16 (72.7)
Black or African American	1 (16.7)	0	1 (20.0)	1 (20.0)	1 (9.1)	3 (13.6)
Unknown	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)

Not Reported	0	1 (16.7)	0	1 (20.0)	2 (18.2)	2 (9.1)
Ethnicity, n (%)						
Hispanic or Latino	0	2 (33.3)	1 (20.0)	1 (20.0)	3 (27.3)	4 (18.2)
Not Hispanic or Latino	6 (100.0)	4 (66.7)	4 (80.0)	4 (80.0)	8 (72.7)	18 (81.8)
Lansky score, n (%)						
50	0	0	0	2 (40.0)	2 (18.2)	2 (9.1)
60	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
70	1 (16.7)	0	0	0	0	1 (4.5)
80	1 (16.7)	0	0	0	0	1 (4.5)
90	1 (16.7)	2 (33.3)	4 (80.0)	0	2 (18.2)	7 (31.8)
100	3 (50.0)	3 (50.0)	0	2 (40.0)	5 (45.5)	8 (36.4)
Karnofsky score, n (%)						
80	0	0	1 (20.0)	0	0	1 (4.5)
90	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)

Assessor's comment

The majority of subjects were white and slightly more than half were male. Most subjects (15/22) were >12 years and no subjects were less than 3 years of age. Thus, there is no information in very young subjects.

Table 4 Baseline Disease Characteristics – Part A1 (Safety Analysis Set)

	Dose Escalation			PK Expansion	Combined	
	1.1 mg/m² (N=6)	**1.4 mg/m² (N=6)**	**1.8 mg/m² (N=5)**	**1.4 mg/m² (N=5)**	**1.4 mg/m² (N=11)**	**Total (N=22)**
Time since diagnosis of primary cancer (month)	n=6	n=6	n=5	n=5	n=11	n=22
Mean (SD)	33.34 (18.271)	20.49 (16.716)	35.33 (30.073)	30.73 (38.060)	25.14 (27.344)	29.69 (25.100)

Median	33.72	11.35	34.92	18.14	12.85	23.59
Min, Max	11.0, 57.7	7.3, 43.5	10.6, 84.4	0.4, 95.8	0.4, 95.8	0.4, 95.8
Age at diagnosis of primary cancer (year)	n=6	n=6	n=5	n=5	n=11	n=22
Mean (SD)	11.65 (4.590)	9.43 (2.526)	10.76 (3.248)	10.55 (6.083)	9.94 (4.282)	10.59 (4.038)
Median	13.25	8.12	10.90	13.34	8.24	11.63
Min, Max	3.4, 15.5	7.2, 12.9	7.1, 14.9	2.3, 17.4	2.3, 17.4	2.3, 17.4
Type of disease being followed for response, n (%)						
Measurable	6 (100.0)	4 (66.7)	4 (80.0)	4 (80.0)	8 (72.7)	18 (81.8)
Evaluable only	0	2 (33.3)	1 (20.0)	1 (20.0)	3 (27.3)	4 (18.2)

Assessor's comment

The majority of subjects had measurable disease. The mean time since the diagnosis of primary cancer was 29.69 months.

Prior medication

Table 5 Previous Anti-Cancer Therapy – Part A1 (Safety Analysis Set)

	Dose Escalation			**PK Expansion**	**Combined**	
	1.1 mg/m² (N=6)	**1.4 mg/m² (N=6)**	**1.8 mg/m² (N=5)**	**1.4 mg/m² (N=5)**	**1.4 mg/m² (N=11)**	**Total (N=22)**
Most recent prior anti-cancer therapy type, n (%)						
Biologic (anti-neoplastic agent)	1 (16.7)	0	1 (20.0)	0	0	2 (9.1)
Chemotherapy Myelosuppressive Therapy	3 (50.0)	0	2 (40.0)	2 (40.0)	2 (18.2)	7 (31.8)
Hematopoietic Growth Factor[a]	1 (16.7)	3 (50.0)	1 (20.0)	3 (60.0)	6 (54.5)	8 (36.4)
Monoclonal Antibodies	1 (16.7)	0	0	0	0	1 (4.5)
Prior Therapy (NOS)	0	2 (33.3)	0	0	2 (18.2)	2 (9.1)

Radiation Therapy	0	1 (16.7)	1 (20.0)	0	1 (9.1)	2 (9.1)
Time since last treatment (month)	n=6	n=6	n=5	n=5	n=11	n=22
Mean (SD)	2.3 (2.58)	4.4 (7.27)	1.1 (0.68)	1.2 (0.31)	3.0 (5.41)	2.3 (4.02)
Median (Min, Max)	1.2 (1, 7)	1.5 (1, 19)	0.8 (1, 2)	1.3 (1, 2)	1.3 (1, 19)	1.1 (1, 19)
Type of prior anti-cancer therapy, n (%)						
Chemotherapy (NOS)	1 (16.7)	0	0	0	0	1 (4.5)
Chemotherapy Multiple Agents Systemic	5 (83.3)	6 (100.0)	5 (100.0)	5 (100.0)	11 (100.0)	21 (95.5)
Chemotherapy Non-Cytotoxic	1 (16.7)	0	0	0	0	1 (4.5)
Chemotherapy Single Agent Systemic	1 (16.7)	0	1 (20.0)	2 (40.0)	2 (18.2)	4 (18.2)
Drug and/or Immunotherapy	2 (33.3)	0	0	0	0	2 (9.1)
Hematopoietic Stem Cell Transplantation	1 (16.7)	0	0	0	0	1 (4.5)
Prior Therapy (NOS)	2 (33.3)	2 (33.3)	1 (20.0)	1 (20.0)	3 (27.3)	6 (27.3)
Radiation Therapy	4 (66.7)	2 (33.3)	2 (40.0)	4 (80.0)	6 (54.5)	12 (54.5)
Surgery	5 (83.3)	6 (100.0)	3 (60.0)	2 (40.0)	8 (72.7)	16 (72.7)

Assessor's comment

All subjects had received prior cancer medication. The median time since last treatment was 1.1 months (range 1 to 19 months).

Concomitant medication

The most frequently reported (>50%) anatomical class of drug were "Nervous System" (21 subjects, 95.5%), "Alimentary Tract and Metabolism" (19 subjects, 86.4%), "Antiinfectives for Systemic Use" (15 subjects, 68.2%), "Opioids" (14 subjects, 63.6%) and "Blood and Blood Forming Organs" (13 subjects, 59.1%).

2.3.2.1.1. Pharmacokinetic results

Average AUC and Cmax in the different dose groups are summarised in Table 1. The average half-life was 35-42 hours in all groups, and mean Cl in the 1.4 mg/m2 group (n=11) was 2110 (SD 923) ml/h.

Table 1. Summary of Pharmacokinetic Parameters of Eribulin Mesylate from Subjects in Part A1 (PK Analysis Set)

	Dose Escalation			PK Expansion	Combined
Parameter	**1.1 mg/m^2 (N=6)**	**1.4 mg/m^2 (N=6)**	**1.8 mg/m^2 (N=5)**	**1.4 mg/m^2 (N=5)**	**1.4 mg/m^2 (N=11)**
$AUC_{(0-t)}$ (h*ng/mL)	n=6	n=6	n=5	n=5	n=11
Mean (SD)	744.0 (353.03)	758.2 (303.38)	1363.0 (1378.53)	1010.8 (538.94)	873.0 (423.80)
Geometric Mean (%CV)	676.1 (50.94)	709.5 (42.14)	1007.6 (94.29)	894.1 (61.10)	788.2 (50.01)
Median	689.5	719.5	886.0	827.0	733.0
Min, Max	418, 1270	367, 1300	484, 3800	448, 1650	367, 1650
$AUC_{(0-inf)}$ (h*ng/mL)	n=3	n=6	n=5	n=4	n=10
Mean (SD)	654.3 (342.72)	830.5 (331.14)	1556.6 (1619.37)	907.8 (493.59)	861.4 (379.11)
Geometric Mean (%CV)	602.6 (51.04)	780.9 (39.58)	1122.6 (100.48)	818.9 (55.05)	795.9 (43.00)
Median	463.0	754.5	936.0	771.5	754.5
Min, Max	450, 1050	445, 1430	512, 4410	488, 1600	445, 1600
$AUC_{(0-inf)}$/D (h*ng/mL/mg)	n=3	n=6	n=5	n=4	n=10
Mean (SD)	498.3 (172.76)	542.7 (151.40)	621.8 (607.69)	595.5 (401.86)	563.8 (259.44)
Geometric Mean (%CV)	474.7 (41.51)	526.8 (26.60)	474.3 (85.67)	500.7 (77.05)	516.2 (46.27)
Median	579.0	487.0	334.0	499.5	487.0
Min, Max	300, 616	405, 795	285, 1700	243, 1140	243, 1140
C_{max} (ng/mL)	n=6	n=6	n=5	n=5	n=11
Mean (SD)	353.8 (59.24)	472.3 (158.23)	382.6 (296.97)	382.8 (247.05)	431.6 (197.78)
Geometric Mean (%CV)	349.9 (16.41)	443.0 (44.63)	321.2 (66.46)	320.5 (77.69)	382.4 (60.09)
Median	339.0	502.5	279.0	380.0	416.0
Min, Max	300, 446	198, 651	193, 909	125, 771	125, 771

Assessor´s comment

Pharmacokinetics of eribulin after the first infusion was characterised in all subjects in the study. The dose groups were small and consisted of children of various age and size. In general, average drug exposure (AUCinf) increased with increased dose.

The Applicant has not discussed the pharmacokinetic parameters in relation to previously observed data from adults.

The Applicant has not presented the exposure or PK parameters in relation to age or BSA, and has not discussed the relevance of the data for smaller children. Indeed, most children in the study were >12 years, and no children <2 years were included. Thus, there is no PK information in small children where maturation of e g transport proteins of importance for eribulin elimination might not be complete.

2.3.2.1.2. Efficacy results

A secondary objective of the study was to assess the antitumor activity of eribulin mesylate in children with refractory or recurrent cancer. Tumour assessment using RECIST 1.1 were performed during the pretreatment phase, at the end of Cycle 1 and then every other cycle for 2 cycles and then every three cycles during the treatment phase for subjects who did not have disease progression. Disease progression and response evaluation were determined by the investigator for each subject according to definitions established in the RECIST Guidelines (version 1.1). Subjects who responded (Complete Response [CR], Partial Response [PR]) to therapy or had long term stable disease (SD) (≥ 6 cycles) on protocol therapy were to be centrally reviewed. For all subjects, overall response while on study was determined by the Study Chair taking into account central review, if applicable. The same imaging methodology was to be used throughout the study.

Tumour response

The majority of subjects (18 subjects) had best overall response of progressive disease.

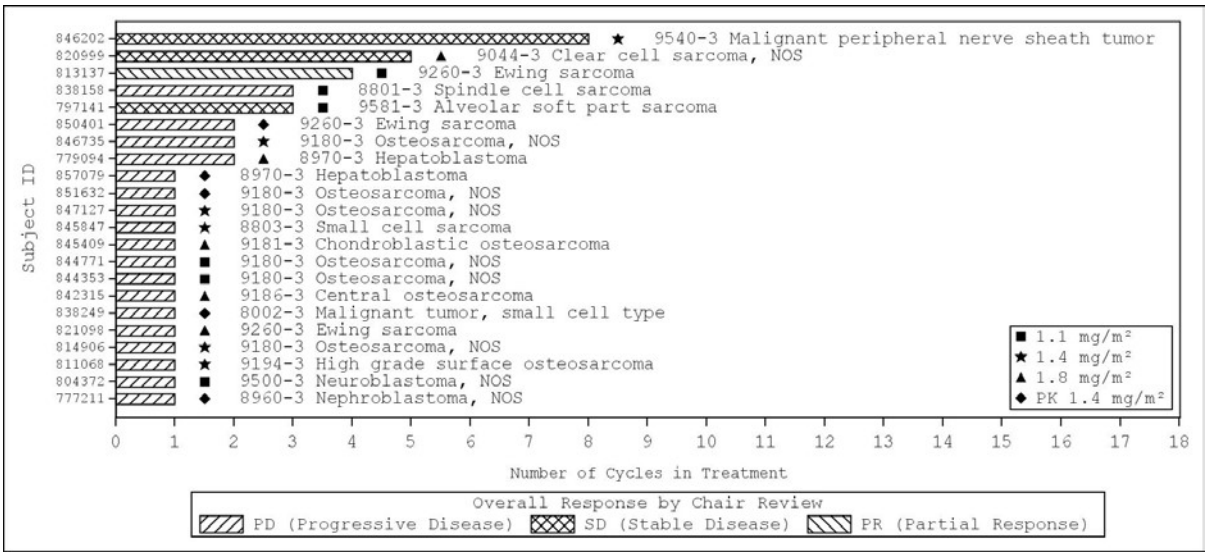
The best overall response was PR for 1 subject and SD for 3 subjects (Figure 1).

• (Dose group 1.1 mg/m2) with Ewing sarcoma had a best overall response of PR (confirmed by central review) and a maximum reduction in SOD from baseline of 70.4%.

• (Dose group 1.4 mg/m2) with Malignant Peripheral Nerve Sheath Tumor (MPNST) had a best overall response of SD (confirmed by central review); this subject had evaluable target lesions only.

• (Dose group 1.1 mg/m2) with alveolar soft part sarcoma had a best overall response of SD and a maximum reduction in SOD from baseline of 6.1%

• (Dose group 1.8 mg/m2) with clear cell sarcoma had a best overall response of SD and a maximum reduction in SOD from baseline of 26.4%.



[HC1]

Figure 1 Overall Response by Study Chair Response Review and Number of Cycles in Treatment – Part A1 (Safety Analysis Set)

Handling of dropout or missing data

Subjects were to be treated until disease progression or withdrawal from the study due to unacceptable toxicity. Subjects may also have withdrawn from the study for reasons other than disease progression or unacceptable toxicity. There was no imputation for missing data.

Assessor's comment

The majority of subjects (18/22) had a best overall response of progressive disease. A partial response was observed for 1 subject (Ewing sarcoma) and stable disease for 3 subjects (Malignant peripheral nerve sheath tumour, alveolar soft part sarcoma and clear cell sarcoma). Considering that this is an open, single armed study investigating different doses in different histologies and with few subjects included it is difficult to draw any firm conclusions regarding efficacy, but overall activity seems low.

No obvious relation between dose and response is noted.

2.3.2.1.3. Safety results

Adverse Events

Dose limiting toxicities

The MTD was defined as the maximum dose at which less than one-third of subjects experienced a DLT during Cycle 1 of therapy.

In the dose-escalation portion of the study, 3 subjects experienced 4 DLTs. None of the 6 subjects in the 1.1 mg/m2 dose cohort experienced a DLT and therefore dose escalation proceeded to the next level. At the next dose level of 1.4 mg/m2 (n=6), 1 subject in this dose cohort experienced 2 DLTs and therefore dose escalation proceeded to the next level. At escalation to the next dose level of 1.8 mg/m2 (n=5), 2 subjects experienced 2 DLTs. It was assessed that eribulin at the dose of 1.8 mg/m2 was not tolerable and hence the previous dose level (eribulin 1.4 mg/m2) was concluded to be the MTD for eribulin.

As the 2 DLTs observed in the subject in the 1.4 mg/m2 dose cohort were different classes of AEs (ie, neutropenia and fatigue), it was considered acceptable to expand the cohort up to 12 subjects (PK expansion).

The DLTs observed in the PK expansion cohort counted towards the total number of DLTs observed at the MTD during the dose escalation portion of the study. If ≥1/3 of the cohort of subjects at the MTD during the dose escalation plus the PK expansion (combined cohort) experienced DLT then the MTD had been exceeded. Only 1 subject in the combined cohort experienced a DLT.

Assessor's comment

No DLTs occurred at the 1.1 mg/m^2 dose level. One subject experienced 2 DLTs at the 1.4 mg/m^2 dose level, fatigue and neutropenia. Two subjects experienced 1 DLT each at the 1.8 mg/m^2 dose level, neutropenia and neutrophil count decreased. Thus, the MTD of eribulin mesylate administered as an IV infusion on Day 1 and Day 8 of a 21 day cycle to children with refractory or recurrent solid tumors including lymphomas, was concluded to be 1.4 mg/m^2.

The age distribution ranged from ≥3 years up to <18 years. Most subjects (15/22) were >12 years. Thus, there is no information in very young subjects.

Summary of Adverse Events

An overall summary of TEAEs is provided for all subjects in Table 6. All subjects reported at least one TEAE and the majority (95.5%) were considered treatment-related by the investigator. Treatment-emergent SAEs were reported by 10 subjects (45.5%) of which 1 subject had a fatal AE (4.5%).

Table 6 Overview of Treatment-Emergent Adverse Events – Part A1 (Safety Analysis Set)

	Dose Escalation			PK Expansion	Combined	
Category	**1.1 mg/m² (N=6) n (%)**	**1.4 mg/m² (N=6) n (%)**	**1.8 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=11) n (%)**	**Total (N=22) n (%)**
Subjects with any TEAEs	6 (100.0)	6 (100.0)	5 (100.0)	5 (100.0)	11 (100.0)	22 (100.0)
Subjects with any treatment-related TEAEs	6 (100.0)	6 (100.0)	5 (100.0)	4 (80.0)	10 (90.9)	21 (95.5)
Subjects with CTCAE Grade 3, 4, or 5 TEAEs	4 (66.7)	6 (100.0)	5 (100.0)	5 (100.0)	11 (100.0)	20 (90.9)
Subjects with TEAEs per action taken						
Protocol treatment discontinued	0	0	0	0	0	0
Protocol treatment delayed	0	1 (16.7)	0	1 (20.0)	2 (18.2)	2 (9.1)
Study dose reduced	0	0	0	0	0	0
Subjects with treatment-emergent SAEs	2 (33.3)	1 (16.7)	3 (60.0)	4 (80.0)	5 (45.5)	10 (45.5)
Subjects with treatment-emergent SAEs of fatal outcome	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
SAE criteria						
Results in death	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
Life threatening	0	0	0	0	0	0
Requires inpatient hospitalization or prolongation of existing hospitalization	2 (33.3)	1 (16.7)	3 (60.0)	2 (40.0)	3 (27.3)	8 (36.4)
Persistent or significant disability or incapacity	0	0	0	0	0	0
Congenital anomaly / birth defect	0	0	0	0	0	0

Important medical event	0	1 (16.7)	0	1 (20.0)	2 18.2)	2 (9.1)

Analysis of Adverse Events

Table 7 Treatment-Emergent Adverse Events With an Incidence of at Least 2 subjects in any Treatment Group – Part A1 (Safety Analysis Set)

	Dose Escalation			PK Expansion	Combined	
Preferred Term	**1.1 mg/m² (N=6) n (%)**	**1.4 mg/m² (N=6) n (%)**	**1.8 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=11) n (%)**	**Total (N=22) n (%)**
WBC count decreased	5 (83.3)	5 (83.3)	5 (100.0)	4 (80.0)	9 (81.8)	19 (86.4)
Lymphocyte count decreased	4 (66.7)	3 (50.0)	3 (60.0)	4 (80.0)	7 (63.6)	14 (63.6)
Anemia	4 (66.7)	4 (66.7)	2 (40.0)	3 (60.0)	7 (63.6)	13 (59.1)
Neutrophil count decreased	5 (83.3)	2 (33.3)	4 (80.0)	2 (40.0)	4 (36.4)	13 (59.1)
Decreased appetite	3 (50.0)	4 (66.7)	2 (40.0)	2 (40.0)	6 (54.5)	11 (50.0)
Nausea	3 (50.0)	3 (50.0)	4 (80.0)	1 (20.0)	4 (36.4)	11 (50.0)
Hemoglobin decreased	3 (50.0)	3 (50.0)	4 (80.0)	0	3 (27.3)	10 (45.5)
AST increased	4 (66.7)	2 (33.3)	2 (40.0)	1 (20.0)	3 (27.3)	9 (40.9)
Headache	2 (33.3)	3 (50.0)	3 (60.0)	1 (20.0)	4 (36.4)	9 (40.9)
Platelet count decreased	1 (16.7)	2 (33.3)	4 (80.0)	2 (40.0)	4 (36.4)	9 (40.9)
Vomiting	3 (50.0)	2 (33.3)	2 (40.0)	2 (40.0)	4 (36.4)	9 (40.9)
ALT increased	3 (50.0)	2 (33.3)	2 (40.0)	1 (20.0)	3 (27.3)	8 (36.4)
Fatigue	2 (33.3)	2 (33.3)	2 (40.0)	2 (40.0)	4 (36.4)	8 (36.4)
Constipation	2 (33.3)	2 (33.3)	3 (60.0)	0	2 (18.2)	7 (31.8)
Non-cardiac chest pain	2 (33.3)	4 (66.7)	1 (20.0)	0	4 (36.4)	7 (31.8)
Pyrexia	0	2 (33.3)	3 (60.0)	2 (40.0)	4 (36.4)	7 (31.8)
Alopecia	1 (16.7)	2 (33.3)	3 (60.0)	0	2 (18.2)	6 (27.3)

Blood sodium decreased	3 (50.0)	2 (33.3)	0	1 (20.0)	3 (27.3)	6 (27.3)
Hypoalbuminemia	1 (16.7)	3 (50.0)	0	2 (40.0)	5 (45.5)	6 (27.3)
Oropharyngeal pain	1 (16.7)	3 (50.0)	1 (20.0)	1 (20.0)	4 (36.4)	6 (27.3)
Pain in extremity	3 (50.0)	1 (16.7)	0	2 (40.0)	3 (27.3)	6 (27.3)
EKG QT prolonged	0	2 (33.3)	1 (20.0)	2 (40.0)	4 (36.4)	5 (22.7)
Hyperglycemia	1 (16.7)	2 (33.3)	1 (20.0)	1 (20.0)	3 (27.3)	5 (22.7)
Hypocalcaemia	1 (16.7)	2 (33.3)	1 (20.0)	1 (20.0)	3 (27.3)	5 (22.7)
Lymphopenia	1 (16.7)	2 (33.3)	1 (20.0)	1 (20.0)	3 (27.3)	5 (22.7)
Musculoskeletal pain	2 (33.3)	2 (33.3)	0	1 (20.0)	3 (27.3)	5 (22.7)
Neutropenia	0	3 (50.0)	1 (20.0)	1 (20.0)	4 (36.4)	5 (22.7)
Proteinuria	0	1 (16.7)	2 (40.0)	2 (40.0)	3 (27.3)	5 (22.7)

	Dose Escalation			**PK Expansion**	**Combined**	
Preferred Term	**1.1 mg/m² (N=6) n (%)**	**1.4 mg/m² (N=6) n (%)**	**1.8 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=11) n (%)**	**Total (N=22) n (%)**
Arthralgia	1 (16.7)	0	2 (40.0)	1 (20.00	1 (9.1)	4 (18.2)
Back Pain	1 (16.7)	1 (16.7)	2 (40.0)	0	1 (9.1)	4 (18.2)
Blood albumin decreased	2 (33.3)	1 (16.7)	0	1 (20.0)	2 (18.2)	4 (18.2)
Blood potassium decreased	0	1 (16.7)	2 (40.0)	1 (20.0)	2 (18.2)	4 (18.2)
Diarrhea	0	2 (33.3)	1 (20.0)	1 (20.0)	3 (27.3)	4 (18.2)
Dyspnea	1 (16.7)	2 (33.3)	0	1 (20.0)	3 (27.3)	4 (18.2)
Hypoesthesia	1 (16.7)	1 (16.7)	0	2 (40.0)	3 (27.3)	4 (18.2)
Hypokalemia	1 (16.7)	1 (16.7)	0	2 (40.0)	3 (27.3)	4 (18.2)
Pruritus	2 (33.3)	0	1 (20.0)	1 (20.0)	1 (9.1)	4 (18.2)
Weight decreased	1 (16.7)	1 (16.7)	2 (40.0)	0	1 (9.1)	4 (18.2)

Cough	0	1 (16.7)	0	2 (40.0)	3 (27.3)	3 (13.6)
Abdominal pain	2 (33.3)	1 (16.7)	0	0	1 (9.1)	3 (13.6)
Hypoxia	1 (16.7)	0	0	2 (40.0)	2 (18.2)	3 (13.6)
Neck pain	2 (33.3)	0	0	1 (20.0)	1 (9.1)	3 (13.6)

Assessor's comment

All subjects experienced at least one TEAE with the vast majority considered related to study drug. The most frequently reported AEs (>50%) were WBC count decrease (86.4%), lymphocyte count decreased (63.6%), anemia (59.1%) and neutrophil count decreased (59.1%). Overall, the safety profile of eribulin treatment in children seems to be similar to that seen in adults.

Grade 3 and 4 Adverse Events

Treatment-emergent AEs with CTCAE Grade 3 and 4 by system organ class reported in at least 2 and preferred term are summarized in Table 8.

Table 8 Treatment-Emergent Adverse Events With CTCAE Grade 3 or 4 by System Organ Class and Preferred Term – Part A1 (Safety Analysis Set)

	Dose Escalation			PK Expansion	Combined	
System Organ Class Preferred Term	**1.1 mg/m² (N=6) n (%)**	**1.4 mg/m² (N=6) n (%)**	**1.8 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=11) n (%)**	**Total (N=22) n (%)**
Subjects with any TEAEs of CTCAE grade 3 or 4	4 (66.7)	6 (100.0)	5 (100.0)	5 (100.0)	11 (100.0)	20 (90.9)
Blood and lymphatic system disorders	0	3 50.0)	1 (20.0)	2 (40.0)	5 (45.5)	6 (27.3)
Anemia	0	1 (16.7)	0	1 (20.0)	2 (18.2)	2 (9.1)
Febrile neutropenia	0	0	1 (20.0)	0	0	1 (4.5)
Leukopenia	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Lymphopenia	0	2 (33.3)	1 (20.0)	1 (20.0)	3 (27.3)	4 (18.2)
Neutropenia	0	3 (50.0)	1 (20.0)	1 (20.0)	4 (36.4)	5 (22.7)
Gastrointestinal disorders	0	0	1 (20.0)	1 (20.0)	1 (9.1)	2 (9.1)
Gingival pain	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)

Nausea	0	0	1 (20.0)	0	0	1 (4.5)
General disorders and administration site conditions	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Fatigue	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Infections and infestations	0	0	1 (20.0)	2 (40.0)	2 (18.2)	3 (13.6)
Device related infection	0	0	1 (20.0)	1 (20.0)	1 (9.1)	2 (9.1)
Lung infection	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
Pneumonia	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
Investigations	4 (66.7)	4 (66.7)	5 (100.0)	3 (60.0)	7 (63.6)	16 (72.7)
ALT increased	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
AST increased	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Blood potassium decreased	0	0	1 (20.0)	1 (20.0)	1 (9.1)	2 (9.1)
Blood urine present	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
Lymphocyte count decreased	4 (66.7)	3 (50.0)	3 (60.0)	3 (60.0)	6 (54.5)	13 (59.1)
Neutrophil count decreased	3 (50.0)	1 (16.7)	3 (60.0)	2 (40.0)	3 (27.3)	9 (40.9)
WBC count decreased	4 (66.7)	2 (33.3)	3 (60.0)	2 (40.0)	4 (36.4)	11 (50.0)
Metabolism and nutrition disorders	3 (50.0)	1 (16.7)	1 (20.0)	0	1 (9.1)	5 (22.7)
Decreased appetite	2 (33.3)	0	0	0	0	2 (9.1)

	Dose Escalation			**PK Expansion**	**Combined**	
System Organ Class Preferred Term	**1.1 mg/m² (N=6) n (%)**	**1.4 mg/m² (N=6) n (%)**	**1.8 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=11) n (%)**	**Total (N=22) n (%)**
Dehydration	0	1 (16.7)	1 (20.0)	0	1 (9.1)	2 (9.1)
Hyponatremia	1 (16.7)	0	0	0	0	1 (4.5)
Musculoskeletal and connective tissue disorders	1 (16.7)	2 (33.3)	0	0	2 (18.2)	3 (13.6)

Back pain	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Musculoskeletal pain	0	2 (33.3)	0	0	2 (18.2)	2 (9.1)
Pain in extremity	1 (16.7)	1 (16.7)	0	0	1 (9.1)	2 (9.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (20.0)	1 (20.0)	1 (9.1)	2 (9.1)
Tumor pain	0	0	1 (20.0)	1 (20.0)	1 (9.1)	2 (9.1)
Nervous system disorders	0	2 (33.3)	0	0	2 (18.2)	2 (9.1)
Hypoesthesia	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Paraesthesia	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Respiratory, thoracic and mediastinal disorders	1 (16.7)	0	0	2 (40.0)	2 (18.2)	3 (13.6)
Cough	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
Dyspnea	1 (16.7)	0	0	0	0	1 (4.5)
Hypoxia	1 (16.7)	0	0	1 (20.0)	1 (9.1)	2 (9.1)
Pleural effusion	1 (16.7)	0	0	0	0	1 (4.5)
Surgical and medical procedures	0	0	1 (20.0)	0	0	1 (4.5)
Central venous catheter removal	0	0	1 (20.0)	0	0	1 (4.5)

ALT = alanine aminotransferase , AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events EKG = electrocardiogram, PK = pharmacokinetic, TEAE = treatment-emergent adverse event, WBC = white blood cell.

Assessor comment:

The majority (90.9%) of subjects reported TEAEs of Grade 3 or 4. All patients in the highest dose groups (1.4 mg/m^2 and 1.8 mg/m^2) experienced Grade 3 and 4 events. The most frequently Grade 3 and 4 AEs were lymphocyte count decreased, WBC count decrease, and neutrophil count decreased. None of the Grade 3 and 4 TEAEs led to discontinuation of the study drug. The Grade 3 and 4 AEs reported are in line with the known safety profile for Eribulin mesylate in adults.

Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths

Table 9 Listing of All Deaths – All Subjects

Subject ID Age(yr.), Sex, Race	System Organ Class / Preferred Term / Verbatim Term	AE Start Date / Study Day (Duration)	Relationship to Study Drug / DLT?	SAE? / Criteria	Action Taken	Study Day of Death
Treatment: PK Expansion 1.4 mg/m²						
14,	Respiratory, thoracic and mediastinal disorders/ Hypoxia/	2015/7 (1)	UNLIKELY/ No	Yes/1	NONE	7

Assessor comment:

One subject died due to SAE of hypoxia on Day 7, 6 days after the last dose of eribulin. However, hypoxia was reported also at baseline for this subject and was considered by the investigator as unlikely related to study drug.

Other Serious Adverse Events

Ten subjects (45.5%) experienced at least one serious TEAE, Table 10. Most SAEs were reported in single subjects with the exception of hypoxia (3 subjects, 13.6%), pain in extremity (2 subjects, 9.1%) and device related infection (2 subjects, 9.1%).

The majority of subjects experienced SAEs that were considered by the investigator to be unrelated to study drug. Three subjects experienced a total of 4 SAE's that were considered by the investigator to be related to study drug: neutropenia (Grade 4), fatigue (Grade 3), pyrexia (Grade 2) and lung infection (Grade 3).

Table 10 Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term – Part A1 (Safety Analysis Set)

	Dose Escalation			PK Expansion	Combined	
System Organ Class Preferred Term	1.1 mg/m² (N=6) n (%)	1.4 mg/m² (N=6) n (%)	1.8 mg/m² (N=5) n (%)	1.4 mg/m² (N=5) n (%)	1.4 mg/m² (N=11) n (%)	Total (N=22) n (%)
Subjects with any treatmentemergent SAEs	2 (33.3)	1 (16.7)	3 (60.0)	4 (80.0)	5 (45.5)	10 (45.5)
Blood and lymphatic system disorders	0	1 (16.7)	1 (20.0)	0	1 (9.1)	2 (9.1)
Febrile neutropenia	0	0	1 (20.0)	0	0	1 (4.5)

Neutropenia	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Gastrointestinal disorders	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
Gingival pain	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
General disorders and administration site conditions	0	1 (16.7)	1 (20.0)	0	1 (9.1)	2 (9.1)
Fatigue	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Pyrexia	0	0	1 (20.0)	0	0	1 (4.5)
Infections and infestations	0	0	1 (20.0)	2 (40.0)	2 (18.2)	3 (13.6)
Device related infection	0	0	1 (20.0)	1 (20.0)	1 (9.1)	2 (9.1)
Lung infection	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
Pneumonia	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
Metabolism and nutrition disorders	0	0	1 (20.0)	0	0	1 (4.5)
Dehydration	0	0	1 (20.0)	0	0	1 (4.5)
Musculoskeletal and connective tissue disorders	1 (16.7)	1 (16.7)	0	0	1 (9.1)	2 (9.1)
Joint swelling	1 (16.7)	0	0	0	0	1 (4.5)
Pain in extremity	1 (16.7)	1 (16.7)	0	0	1 (9.1)	2 (9.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (20.0)	0	0	1 (4.5)
Tumor pain	0	0	1 (20.0)	0	0	1 (4.5)
Nervous system disorders	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Hypoesthesia	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Paraesthesia	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
Respiratory, thoracic and mediastinal disorders	1 (16.7)	0	0	2 (40.0)	2 (18.2)	3 (13.6)
Dyspnea	1 (16.7)	0	0	0	0	1 (4.5)

	Dose Escalation	**PK Expansion**	**Combined**	

System Organ Class Preferred Term	1.1 mg/m^2 (N=6) n (%)	1.4 mg/m^2 (N=6) n (%)	1.8 mg/m^2 (N=5) n (%)	1.4 mg/m^2 (N=5) n (%)	1.4 mg/m^2 (N=11) n (%)	Total (N=22) n (%)
Hypoxia	1 (16.7)	0	0	2 (40.0)	2 (18.2)	3 (13.6)
Laryngeal hemorrhage	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)
Pleural effusion	1 (16.7)	0	0	0	0	1 (4.5)
Tachypnea	0	0	0	1 (20.0)	1 (9.1)	1 (4.5)

PK = pharmacokinetic.

A subject with two or more adverse events in the same system organ class or preferred term is counted only once for that system organ class or preferred term.

Assessor comment:

Slightly less than half (10/22) of the patients reported at least one SAE. It is noted that there were three cases of hypoxia; all considered by the investigator as unlikely/unrelated to study drug. Overall, no new safety signals were detected compared with the safety profile in adults.

For further discussion on selected AEs, see below.

Other Significant Adverse Events

Adverse events that resulted in discontinuation of study drug

No TEAE resulting in study drug discontinuation were reported in this study.

Adverse events that required study drug dose adjustment or interruption

No TEAE resulting in a dose reduction of study drug were reported in this study.

Treatment-Emergent AEs resulting in eribulin mesylate dose delay occurred in 2 subjects (9.1%). One subject in the 1.4 mg/m2 dose escalation group reported fatigue and 1 subject in the 1.4 mg/m2 PK expansion groups reported a lung infection.

Study drug overdose, misuse, abuse or medication error

No TEAE resulting in study drug discontinuation were reported.

Assessor's comment

There were no patients that had a study drug discontinuation or a dose reduction due to an AE. Two subjects, both in the 1.4 mg/m^2 dose cohort, had an AE that resulted in a dose delay; one subject reported fatigue and one subject reported a lung infection.

Other clinically significant events

Adverse events of alopecia, neutropenia, and peripheral neuropathy, commonly seen with cytotoxic chemotherapy, are summarized in this section.

Alopecia was reported in 6 subjects (27.3%). All were non-serious and considered by the investigator to be related to study treatment.

Neutrophil count decreased and neutropenia were reported in 13 subjects (59.1%) and 5 subjects (22.7%), respectively. All events were considered by the investigator to be related to study treatment. Grade 3 or 4 neutrophil count decreased was reported in 9 subjects (40.9%) and none were reported as serious. Fifteen subjects (68.2%) had a Grade 3 or 4 ANC nadir with time to recovery to Grade ≤2 of between 3 and 12 days (Listing 16.2.8.3). Grade 3 or 4 neutropenia was reported in 5 subjects (22.7). Of these, 1 subject had an SAE of Grade 4 neutropenia. The event was reported as an "important medical event" and resolved. An SAE of CTCAE Grade 3 febrile neutropenia was reported in 1 subject and considered by the investigator to be treatment related. The event resulted in hospitalization and was reported as resolved.

Although there were no events of peripheral neuropathy reported, TEAEs of dysgeusia (1 subject), hypoesthesia (4 subjects) and paraesthesia (3 subjects) were reported Of these 1 subject reported an SAE of Grade 3 hypoesthesia and 1 subject reported an SAE of Grade 2 paraesthesia; both events were considered by the investigator as unrelated to study treatment and resolved.

Assessor's comment

There were no reports of peripheral neuropathy reported. However, dysgeusia was reported in 1 subject, hypoaesthesia was reported in 4 subjects and paraesthesia was reported in 3 subjects. Peripheral neuropathy is a known adverse effect of eribulin.

No new safety signals were detected compared with the safety profile in adults.

Clinical laboratory evaluation

Evaluation of each laboratory parameter

Laboratory parameters over time

There were no changes of clinical importance in mean laboratory values over time.

Individual Subject Changes: Shifts From Baseline

Observations in the shift analysis were consistent with the expected safety profile of eribulin.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs

There were no changes of clinical importance in mean vital signs over time.

Electrocardiograms

Table 11 Summary of Abnormal QTC Results – Part A1 (Safety Analysis Set)

	Dose Escalation			PK Expansion	Combined	
Category	**1.1 mg/m² (N=6) n (%)**	**1.4 mg/m² (N=6) n (%)**	**1.8 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=5) n (%)**	**1.4 mg/m² (N=11) n (%)**	**Total (N=22) n (%)**
Subjects with baseline and postbaseline data	6 (100.0)	6 (100.0)	5 (100.0)	5 (100.0)	11 (100.0)	22 (100.0)
At least one post-baseline increase						

>30 msec	1 (16.7)	1 (16.7)	1 (20.0)	0	1 (9.1)	3 (13.6)
>60 msec	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
At least one post-baseline value						
>450 msec	0	2 (33.3)	1 (20.0)	2 (40.0)	4 (36.4)	5 (22.7)
>480 msec	0	1 (16.7)	0	0	1 (9.1)	1 (4.5)
>500 msec	0	0	0	0	0	0

Assessor's comment

QT prolongation is described in the SmPC for adults.

2.3.3. **Discussion on clinical aspects**

This application concerns a paediatric phase I study E7389-A001-113 A (A Phase 1 Study of Eribulin Mesylate, a Novel Microtubule Targeting Chemotherapeutic Agent in Children with Refractory or Recurrent Solid Tumors (Excluding CNS), Including Lymphomas) which has been conducted and completed as by the agreed paediatric investigations plan.

The study included 22 subjects that received at least one dose of eribulin mesylate. Information from this study was intended to help determine appropriate dosing in children with refractory or recurrent solid tumours, and to evaluate safety, toxicity and pharmacokinetics (PK). The MTD for eribulin was concluded to be 1.4 mg/m^2.

Pharmacokinetics of eribulin after the first infusion was characterised in all subjects. No conclusions were drawn. The Applicant did not discuss the pharmacokinetic parameters in relation to previously observed adult PK data and did not present the exposure or PK parameters in relation to age or BSA. Of note, most children were >12 years old and no data is available in children <2 years.

The majority of subjects (18 subjects) had progressive disease. The best overall response was PR for 1 subject and SD for 3 subjects. Considering that this is an open, single armed study investigating different doses in different histologies and with few subjects included it is difficult to draw any firm conclusions regarding efficacy, but overall activity seems low.

The number of paediatric subjects where upon the characterisation of the eribulin mesylate safety profile rests may be considered limited however **t**he safety profile of eribulin treatment in children seems to be similar to that seen in adults.

No new efficacy or safety information that justifies regulatory action has been identified.

3. **Rapporteur's overall conclusion and recommendation**

The MTD for eribulin was concluded to be 1.4 mg/m^2. No new efficacy or safety information that justifies regulatory action has been identified.

☒ **Fulfilled:**

No regulatory action required.