27 January 2022
EMA/122348/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Halaven

eribulin

Procedure no: EMEA/H/C/002084/P46/026

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	29 Nov 2021	29 Nov 2021	☐
☐	CHMP Rapporteur Assessment Report	03 Jan 2022	09 Dec 2021	☐
☐	CHMP members comments	17 Jan 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Jan 2022	n/a	☐
☒	CHMP adoption of conclusions:	27 Jan 2022	27 Jan 2022	☐

Table of contents

1. Introduction

On 15th November 2021, the MAH submitted a completed paediatric study for eribulin (Halaven), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

It is noted that the MAH has recently submitted a type II variation (EMEA/H/C/002084/II/0060) to update the SmPC based on data from paediatric studies, including Study E7389-G000-213, which is the subject of the current Article 46 procedure, and Studies E7389-G000-223 and E7389-A001-113, which were the subjects of previous Article 46 procedures (MEA/H/C/002084/P46/025; finalised October 27, 2021 and EMEA/H/C/208/P46/023; finalised June 2019, respectively).

2. Scientific discussion

2.1. Information on the development program

The MAH confirms that Study E7389-G000-213 is part of the clinical development program for eribulin and is Study 8 in the approved Paediatric Investigation Plan (EMEA-001261-PIP01-11-M06).

A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Halaven 0.44 mg/mL solution for infusion.

Irinotecan hydrochloride 20 mg/ml solution for infusion.

2.3. Clinical aspects

2.3.1. Methods

Study E7389-G000-213 (Study 213) was a Phase 1/2 open-label, single-arm, multicentre study of eribulin mesilate in a paediatric population with refractory/recurrent solid tumours; an Eisai-sponsored clinical study, which recently completed enrolment as part of a clinical development program.

The primary aim of the **Phase 1** portion of the study was to determine the maximum tolerated dose (MTD) / recommended Phase 2 dose (RP2D) of eribulin mesilate in combination with weekly and daily irinotecan hydrochloride in paediatric subjects with relapsed/refractory solid tumours, excluding the central nervous system (CNS).

The primary aim of the **Phase 2** portion of the study was to assess the objective response rate (ORR) and duration of response (DOR) of eribulin mesilate in combination with irinotecan hydrochloride in paediatric subjects with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and Ewing sarcoma (EWS).

Secondary objectives included assessment of safety and tolerability, PFS and pharmacokinetics. Eligible subjects were male or female, aged ≥12 months to ≤25 years; further in Phases 1 and 2, subjects aged >6 months and <12 months with a performance score ≥50 in Karnofsky scale or Lansky scale were enrolled (at a lower dose level).

The study consisted of 3 phases: Pre-treatment Phase (Days -28 to -1), a Treatment Phase (21-day treatment cycle), and a Follow-up Period. In the Pre-treatment Phase, computed tomography (CT)/magnetic resonance imaging (MRI) scans were performed within 28 days before study drug administration. Clinical and laboratory test results were also performed to determine eligibility within 7 days before study drug administration, unless otherwise indicated.

The Treatment Phase started on Day 1 of Cycle 1. In Phase 1, eribulin mesilate was administered at a dose of 1.4 mg/m^2 by intravenous (IV) infusion on Days 1 and 8 of each 21-day cycle in combination with irinotecan hydrochloride administered by IV infusion on either Days 1 to 5 of a 21-day cycle (Schedule A), or Days 1 and 8 of a 21-day cycle (Schedule B). In Phase 2, Schedule A Dose Level 1 (eribulin 1.4 mg/m^2 Days 1 and 8 with irinotecan 40 mg/m^2 Days 1 to 5 of a 21- day cycle) from Phase 1 was selected as the RP2D for the Phase 2 portion of this study.

Subjects could continue to receive study treatment for up to 1 year from the start of study as long as they were still receiving clinical benefit and had not experienced intolerable toxicity. After 1 year, any continued treatment was to be discussed with the sponsor.

The Follow-up Period began immediately after end of treatment. After discontinuation from study treatment and completing the off-treatment visit, subjects were followed up at least 4 weeks later (i.e., greater than or equal to 28 days after the last dose but no longer than 1 year) unless consent was withdrawn. Subjects who discontinued treatment without objective evidence of disease progression continued to have tumour assessments performed until disease progression, death, or another anticancer therapy was initiated, whichever occurred first, unless the study was terminated. These follow-up data were required unless consent was withdrawn.

In Phase 2, a futility analysis was performed in which 9 subjects per histology group (RMS, NRSTS, and EWS) were enrolled and treated at the RP2D. As per protocol, the futility analysis threshold for histology cohort expansion was at least 3 confirmed responses (PR or complete response [CR]) in each histology.

Safety assessments consisted of monitoring and recording all AEs/serious adverse events (SAEs) (including study-specific events of special interest), according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grades (for both increasing and decreasing severity); regular monitoring of haematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; performance status; and performance of physical examinations.

Events of special interest for this study included neutrophil count decreased and neutropenia, alopecia, peripheral neuropathy, osteonecrosis of the jaw, pain in the jaw, QT prolongation, sepsis, and diarrhoea.

All AEs were to be followed until resolution or for 28 days after the subject's last dose of study medication, whichever came first. SAEs were to be collected for 28 days posttreatment and followed until resolution or, if resolution is unlikely, until the event or sequelae stabilize.

The determination of MTD and RP2D was based on a review of the outcomes of safety (including DLTs), tumour assessments and pharmacokinetics (PK) in Phase 1 by the study investigators and the study team. Following data review, there were no notable differences in the safety, efficacy and PK results between Schedule A and Schedule B. After independent expert recommendations and consultation with the study investigators, the Schedule A MTD (eribulin 1.4 mg/m^2 and irinotecan 40 mg/m^2) was determined as the R2PD.

This study was sponsored and conducted by Eisai.

2.3.2. Disposition/Analysis Set

Subjects were enrolled from 05 Mar 2018 to 16 Mar 2021 across 22 sites in France, Germany, Greece, Italy, Poland, Spain, and the UK. Forty-six subjects were screened for entry into the study. Of these, 13 subjects were enrolled in Phase 1 and 28 were enrolled in Phase 2; all subjects in Phase 1 and 27 subjects in Phase 2 were treated. All subjects discontinued study drug.

Phase 1

All 13 subjects enrolled in Phase 1 received study drug. For Schedule A, 3 subjects received eribulin 1.4 mg/m^2 and irinotecan 20 mg/m^2, and 4 subjects received eribulin 1.4 mg/m^2 and irinotecan 40 mg/m^2. For Schedule B, 3 subjects received eribulin 1.4 mg/m^2 and irinotecan 100 mg/m^2, and 3 subjects received eribulin 1.4 mg/m^2 and irinotecan 125 mg/m^2. All 13 subjects discontinued study drug and are off study. The primary reason for study drug discontinuation was radiological disease progression in 10 subjects (76.9%). Other primary reasons for study drug discontinuation were clinical disease progression, subject's choice to discontinue study drug and other reason (principal investigator's [PI's] decision to surgically remove the tumour) in 1 subject each (7.7%). No subject discontinued study drug because of a COVID-19-related reason. As of 09 Jul 2021, 5 subjects had died, 7 subjects were alive, and 1 subject withdrew consent.

Demographics of the Phase 1 subjects is summarised in Table 1. With the exception of 1 subject with a Lansky performance status (PS) score of 70, all subjects had a Lansky or Karnofsky PS score of 80 or above at Baseline.

Table 1. Demographics – Phase 1

Category	Schedule A		Schedule B		Total
	E1.4 + I20 (N=3)	E1.4 + I40 (N=4)	E1.4 + I100 (N=3)	E1.4 + I125 (N=3)	(N=13)
Country, n (%)					
Germany	1 (33.3)	0 (0.0)	2 (66.7)	0 (0.0)	3 (23.1)
Greece	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.7)
Italy	2 (66.7)	2 (50.0)	1 (33.3)	1 (33.3)	6 (46.2)
Spain	0 (0.0)	1 (25.0)	0 (0.0)	2 (66.7)	3 (23.1)
Age (years)					
Mean (SD)	10.94 (6.583)	7.33 (2.540)	13.97 (4.231)	8.06 (4.997)	9.87 (4.842)
Median	12.42	7.33	15.25	6.42	9.25
Q1, Q3	3.75, 16.67	5.58, 9.08	9.25, 17.42	4.08, 13.67	6.42, 13.67
Min, max	3.8, 16.7	4.3, 10.4	9.3, 17.4	4.1, 13.7	3.8, 17.4
Age Group, n (%)					
≥2 to <12 years	1 (33.3)	4 (100.0)	1 (33.3)	2 (66.7)	8 (61.5)
≥12 to <18 years	2 (66.7)	0 (0.0)	2 (66.7)	1 (33.3)	5 (38.5)
Sex, n (%)					
Male	1 (33.3)	3 (75.0)	1 (33.3)	1 (33.3)	6 (46.2)
Female	2 (66.7)	1 (25.0)	2 (66.7)	2 (66.7)	7 (53.8)
Race, n (%)					
White	3 (100.0)	4 (100.0)	2 (66.7)	3 (100.0)	12 (92.3)
Asian	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (7.7)
Other Asian	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (7.7)
Ethnicity, n (%)					
Hispanic/Latino	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (7.7)
Not Hispanic/Latino	3 (100.0)	3 (75.0)	3 (100.0)	3 (100.0)	12 (92.3)

Phase 2

Of the 28 subjects enrolled into Phase 2 of the study (9 subjects in each RMS and NRSTS histology cohort and 10 subjects in the EWS histology cohort), 1 subject in the EWS histology cohort did not receive any study drug and was not included in any analysis set after the subject chose not to continue in the study. All 27 subjects discontinued study drug and are off study. The primary reason for discontinuation was radiological disease progression in 19 subjects (70.4%); adverse events (AEs) in 3 subjects (11.1%; 1 subject had a treatment- emergent adverse event (TEAE) of low mood; 1 subject had a TEAE of peripheral sensorimotor neuropathy, and 1 subject had a TEAE of thrombocytopenia); and other reasons (investigator's decision, clinician's decision, clinical progression in 1 subject each) in 3 subjects (11.1%). Finally, 2 subjects (7.4%) discontinued study drug due to clinical disease progression. No subject discontinued study drug because of a COVID-19 related cause. As of 09 Jul 2021, 4 subjects in the RMS and 3 subjects each in the NRSTS and EWS histology groups had died, and 17 subjects were alive.

Demographics of the Phase 1 subjects is summarised in Table 2Table 1. With the exception of 2 subjects (1 subject each in the NRSTS and EWS cohort) with a Lansky PS score of 60, all subjects had Lansky or Karnofsky PS score of 70 or above at Baseline.

For both phases, the Full Analysis Set and the Safety Analysis Set consisted of subjects who received at least 1 dose of either study drug.

The Pharmacokinetic Analysis Set included subjects who had documented dosing history and at least 1 post-dosing quantifiable drug concentration. The Dose Evaluable Set (Phase 1 only) consisted of all subjects who completed Cycle 1 treatment and were evaluated for dose-limiting toxicities (DLTs) and those who discontinued during Cycle 1 due to a DLT.

Table 2. Demographics - Phase 2

Category	RMS (N=9)	NRSTS (N=9)	EWS (N=9)	Total (N=27)
Country, n (%)				
France	3 (33.3)	0 (0.0)	1 (11.1)	4 (14.8)
Italy	2 (22.2)	3 (33.3)	1 (11.1)	6 (22.2)
Poland	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.7)
Spain	2 (22.2)	3 (33.3)	6 (66.7)	11 (40.7)
UK	2 (22.2)	2 (22.2)	1 (11.1)	5 (18.5)
Age (years)				
Mean (SD)	11.05 (3.845)	12.71 (4.348)	11.59 (3.753)	11.78 (3.899)
Median	11.58	14.58	12.00	12.08
Q1, Q3	9.67, 12.75	10.17, 15.75	10.42, 14.33	9.67, 14.58
Min, max	4.2, 17.2	4.7, 16.6	4.3, 16.3	4.2, 17.2
Age group, n (%)				
≥2 to <12 years	5 (55.6)	3 (33.3)	4 (44.4)	12 (44.4)
≥12 to <18 years	4 (44.4)	6 (66.7)	5 (55.6)	15 (55.6)
Sex, n (%)				
Male	4 (44.4)	7 (77.8)	4 (44.4)	15 (55.6)
Female	5 (55.6)	2 (22.2)	5 (55.6)	12 (44.4)
Race, n (%)				
White	5 (55.6)	8 (88.9)	8 (88.9)	21 (77.8)
Black or African American	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.7)
Other	2 (22.2)	0 (0.0)	0 (0.0)	2 (7.4)
Missing	2 (22.2)	0 (0.0)	1 (11.1)	3 (11.1)
Ethnicity, n (%)				
Hispanic/Latino	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.7)
Not Hispanic/Latino	9 (100.0)	8 (88.9)	9 (100.0)	26 (96.3)

2.3.3. Efficacy results

Efficacy assessment was not an objective in Phase 1; preliminary tumour responses were explored for the determination of RP2D for the study. Two subjects in Schedule A had PRs, one of which was confirmed.

The primary efficacy endpoint in Phase 2 was objective response determined by the investigator per RECIST 1.1. Of the 27 subjects treated, 3 subjects had confirmed PR (1 subject in each of the RMS, NRSTS, and EWS histology cohorts). The ORR was 11.1%. The duration of response (DOR) for each of the 3 responders was 2.86 months (RMS), 1.41 months (NRSTS), and 15.38 months (EWS). The median progression-free survival (PFS) per RECIST 1.1 as assessed by the investigator was 2.66 months overall and the clinical benefit rate (CBR) was 48.1% (Table 3).

Table 3. Summary of Tumour Response – Phase 2 (FAS)

	RMS (N=9) n (%)	NRSTS (N=9) n (%)	EWS (N=9) n (%)	Total (N=27) n (%)
Best Overall Response (BOR)				
Complete Response (CR), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response (PR), n (%)	1 (11.1)	1 (11.1)	1 (11.1)	3 (11.1)
Stable Disease (SD), n (%)	4 (44.4)	2 (22.2)	5 (55.6)	11 (40.7)
Progressive Disease (PD), n (%)	4 (44.4)	4 (44.4)	3 (33.3)	11 (40.7)
Not Evaluable[a], n (%)	0 (0.0)	2 (22.2)	0 (0.0)	2 (7.4)
Objective Response (CR + PR), n (%)	1 (11.1)	1 (11.1)	1 (11.1)	3 (11.1)
90% CI of ORR[b]	0.6, 42.9	0.6, 42.9	0.6, 42.9	3.1, 26.3
Clinical Benefit (CR + PR + durable SD), n (%)	5 (55.6)	3 (33.3)	5 (55.6)	13 (48.1)
90% CI of CBR[b]	25.1, 83.1	9.8, 65.5	25.1, 83.1	31.3, 65.3

Data cutoff date: 09 Jul 2021.
The tumor assessment was based on RECIST 1.1 criteria.
The clinical benefit is defined as best overall response of CR, PR, or durable SD based on RECIST 1.1, where durable SD is defined as SD with duration longer than 11 weeks.
CBR = clinical benefit rate, EWS = Ewing sarcoma, FAS = Full Analysis Set, NRSTS = non-rhabdomyosarcoma soft tissue sarcoma, ORR = objective response rate, RMS = rhabdomyosarcoma, SD = stable disease.
a: One subject had SD early (<5 weeks) and 1 subject had no post-baseline tumor assessment due to disease progression.
b: The 90% CI was calculated using exact (Clopper-Pearson) 2-sided 90% confidence limits.

Futility analysis

A futility analysis of efficacy was performed after data from the first 9 subjects per histology cohort were available. Enrolment was paused while the analysis was conducted, and the study was then stopped as there were fewer than 3 confirmed responses in each of the histology cohorts (1 confirmed PR observed in each histology cohort).

2.3.4. Safety results

All subjects in Phase 1 and Phase 2 had at least 1 TEAE. The safety outcomes of combined eribulin and irinotecan administration in these paediatric subjects were generally consistent with the known safety profile of either study drug as monotherapy from previous clinical experience in paediatric subjects and

in the adult population. The COVID-19 pandemic did not have any known impact on the safety outcomes of this study.

Phase 1

- None of the 13 subjects in either dosing schedule experienced any DLTs.
- The most commonly reported TEAEs (≥20% of subjects) were neutropenia, anaemia, vomiting, leukopenia, neutrophil count decreased, nausea, pyrexia, white blood cell count decreased, upper abdominal pain, headache, and thrombocytopenia. There were no reported TEAEs related to COVID-19.
- TEAEs of ≥Grade 3 occurred in 12 subjects. The most commonly reported (≥20% of subjects) ≥ Grade 3 TEAEs were neutropenia, leukopenia, neutrophil count decreased, and white blood cell count decreased. Four of the 5 subjects with neutrophil count decreased had at least 1 event of white blood cell count decreased.
- Treatment-related TEAEs were reported in all 13 subjects. Twelve subjects had TEAEs of Grade 3 or higher; the most commonly reported (≥20% of subjects) were neutropenia, leukopenia, neutrophil count decreased, and white blood cell count decreased.
- Overall, 5 of 13 subjects had at least 1 SAE reported (including fatal SAEs). The fatal SAEs were reported in 2 subjects and were malignant neoplasm progression. The most commonly reported SAEs were pyrexia (3 subjects) and malignant neoplasm progression (2 subjects).
- There were no subjects with TEAEs that led to discontinuation of either eribulin or irinotecan in Phase 1.

Phase 2

- The most common TEAEs (≥20% of subjects) were diarrhoea, neutrophil count decreased, anaemia, abdominal pain, nausea, neutropenia, vomiting, pyrexia, decreased appetite, and fatigue. One subject was diagnosed with a Grade 3 TEAE of COVID-19.
- TEAEs of ≥Grade 3 were reported in all 27 subjects. The most commonly reported ≥Grade 3 TEAEs (≥20% of subjects) were neutrophil count decreased and neutropenia.
- Treatment-related TEAEs were reported in 26 subjects. Twenty-four subjects had treatment-related TEAEs of Grade 3 or higher; the most commonly reported (≥20% of subjects) were neutrophil count decreased, and neutropenia.
- Overall, 12 of 27 subjects had at least 1 SAE reported (including fatal SAEs). The fatal SAEs were reported in 5 subjects and were malignant neoplasm progression (3 subjects), malignant pleural effusion (1 subject), and abdominal pain (1 subject; related to disease progression). The most commonly reported SAEs were malignant neoplasm progression (3 subjects), febrile neutropenia, and malignant pleural effusion (each in 2 subjects).
- Four subjects in Phase 2 had TEAEs that led to discontinuation of both study drugs. The events were thrombocytopenia, peripheral sensorimotor neuropathy, malignant pleural effusion, and depressed mood (all events [with the exception of malignant pleural effusion] were assessed as related to study drug).
- As AEs of alopecia, neutropenia, and peripheral neuropathy can be noted with cytotoxic chemotherapy such as eribulin, the following provides a summary of the findings within this study.

- All 13 subjects in Phase 1 had Grade 3 or higher TEAEs of special interest of neutropenia and neutrophil count decreased. Other reported TEAEs of special interest were alopecia and diarrhoea. None of the events of special interest were an SAE.
- Twenty-one subjects in Phase 2 had TEAEs of neutropenia and neutrophil count decreased of Grade 3 or higher. Other reported TEAEs of special interest were alopecia, diarrhoea, pain in jaw, sepsis, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, neuralgia, and ECG QT prolongation. Except from the events of pain in jaw and sepsis, none of the other events of special interest was rated as an SAE.

Pharmacokinetic Analyses and Results

In Phase 1, plasma concentrations of eribulin, and irinotecan and its active metabolite SN-38 were tabulated and summarized by dose level, day, and time. The PK parameters for eribulin, irinotecan, and SN-38 were derived from plasma concentrations by noncompartmental analysis using actual times. In Phase 2, the PK data were assessed using a population pharmacokinetic (PopPK) approach using nonlinear mixed effect modelling. Eribulin, irinotecan, and SN-38 (active metabolite for irinotecan) exposures in Phase 1 were approximately similar between schedules and dose levels. The PK parameters of eribulin appear similar to the values reported from previous clinical experience at the 1.4 mg/m2 dose for eribulin. The PK parameters of irinotecan and its active metabolite SN-38 maximum observed concentration and terminal elimination phase half-life appear similar, while the area under the curve value was less than the reported values in the irinotecan prescribing information.

A pooled PopPK and PK/pharmacodynamic exposure-response analysis for safety and efficacy will be performed and presented in a separate, standalone report (CPMSE7389008R_v1). This PopPK report will include the data from Phase 1 and Phase 2 studies (Studies E7389-A000-113, E7389-G000-213, and E7389-G000-223).

Assessor's note: Pharmacokinetic data will be discussed within the ongoing type II variation (II/60) aiming at updating the Halaven SmPC with paediatric data.

2.3.5. MAH's Overall Conclusions in the Context of the Article 46 Submission

In Phase 1 of study 213, no DLTs were observed at any dose level or in either study treatment schedule. The data from the Phase 1 portion of the study showed that there was a tolerable safety profile in both schedules with similar PK profiles; 2 PRs were noted in Schedule A, 1 of which was confirmed. Based on the data review by the study team and following independent expert recommendations and consultation with the study investigators, Schedule A (eribulin 1.4 mg/m2 on Day 1 and Day 8 with irinotecan 40 mg/m2 on Days 1 to 5 of a 21-day cycle) was selected as the RP2D.

In Phase 2, three of 27 subjects enrolled and treated achieved a confirmed PR (1 subject of each of the 9 subjects treated per histology RMS, EWS and NRSTS) before the futility analysis. This study had a predefined target of 3 or more confirmed responses (PR or CR) per histology to continue enrolment. Following the futility analysis and the observation of only 1 confirmed PR per histology, enrolment into all 3 histologies was discontinued and the study ended.

These results do not support further continued clinical development of eribulin in combination with irinotecan as potential antitumour treatment strategy in paediatric subjects with refractory or recurrent solid tumours. The safety outcomes of combined eribulin and irinotecan administration in these paediatric subjects were generally consistent with the known safety profile of either study drug as

monotherapy from previous clinical experience in paediatric subjects and in the adult population. No new safety signals were identified with the combination treatment.

2.3.6. Discussion on clinical aspects

In Study 213, eribulin in combination with irinotecan demonstrated low activity in paediatric subjects with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and Ewing sarcoma (EWS). At the futility analysis, there were altogether three objective responses (all PR) among the 27 subjects included in the Phase 2 part of the study (11.1%). The duration of response was short in two of three subjects with PR: 2.86 months (RMS), 1.41 months (NRSTS), and 15.38 months (EWS). The study was terminated, according to protocol.

In a previously submitted study of eribulin monotherapy in paediatric sarcomas, Study E7389-G000-223 (Study 223), which was discussed in the Article 46 procedure MEA/H/C/002084/P46/025, no responses were seen. It cannot therefore be excluded that the small effect observed in the current Study 213 was primarily induced by irinotecan. Altogether, the MAH's conclusions are endorsed; the efficacy data from Study 213 do not warrant further investigation of eribulin in combination with irinotecan in paediatric subjects with RMS, NRSTS or EWS.

Assessment of safety data from Study 213 is somewhat hampered by the small number of subjects and the lack of comparator arm. Nevertheless, the safety results were as expected from the known safety profiles of eribulin and irinotecan. The most common TEAEs were, thus, diarrhoea, neutrophil count decreased, white blood cell count decreased, anaemia, abdominal pain, nausea, neutropenia, vomiting, pyrexia, decreased appetite, headache and fatigue. The most commonly reported ≥Grade 3 TEAEs were neutrophil count decreased and neutropenia. SAEs were reported in five of the 13 subjects in Phase 1 and in 12 of the 27 subjects in Phase 2. In seven cases the SAE was fatal. All fatal SAEs and many of the non-fatal SAEs were assessed as disease progression. Other SAEs were febrile neutropenia, pyrexia, bacteraemia, sepsis, upper respiratory tract infection, malnutrition, pain in jaw, device-related infection, dyspnoea. Altogether, the safety data from the study does not give raise to new safety concerns for eribulin.

2.3.6.1. Product information

Currently, the Halaven SmPC states the following regarding paediatric use:

> ***Section 4.2***
>
> *Paediatric population*
>
> *There is no relevant use of HALAVEN in children and adolescents for the indication of breast cancer.*
>
> *The safety and efficacy of HALAVEN in children from birth to 18 years of age have not yet been established in soft tissue sarcoma. No data are available.*
>
> ***Section 5.1***
>
> *Paediatric population*
>
> *The European Medicines Agency has waived the obligation to submit the results of studies with eribulin in all subsets of the paediatric population in the indication of breast cancer (see section 4.2 for information on paediatric use).*
>
> *The European Medicines Agency has deferred the obligation to submit the results of studies with HALAVEN in one or more subsets of the paediatric population for the treatment of*

rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma. See section 4.2 for information on paediatric use.

According to Articles 16 and 17 of Regulation (EC) No 726/2004, results from paediatric studies, even when there is lack of activity, should be included in the SmPC to provide guidance for the prescribers. The rapporteur therefore suggests that the SmPC, section 5.1 should be updated with the efficacy data from Study 213.

In a recent Art. 46 procedure (MEA/H/C/002084/P46/025; finalised October 27, 2021), the MAH submitted the final report of Study 223, evaluating the efficacy of eribulin as monotherapy in paediatric sarcomas. In the CHMP AR (dated September 17, 2021) it was concluded that the MAH should either submit a variation to update the SmPC to reflect the results of Study 223 or provide a justification for not doing so. The following updates were recommended:

- Section 5.1 of the SmPC should be updated with a brief description of the results of Study 223 (number of patients, the diagnoses included and that no responses were seen).
- The current deferral information in section 5.1 should be updated to reflect finalisation of the study.
- Section 4.2 (paragraph on paediatric soft tissue sarcoma) should be updated by replacing the text 'No data are available' with a reference to section 5.1.

Accordingly, the MAH has recently submitted a type II variation (EMEA/H/C/002084/II/0060) aiming at updating the SmPC with the results of paediatric studies (efficacy and pharmacokinetic data) including Study 223, Study 213 and Study 113, which was the subject of a previous Article 46 procedure in 2019. The text proposals will be assessed and discussed within the variation procedure.

3. Rapporteur's overall conclusion and recommendation

The efficacy results of Study 213 do not support further clinical development of eribulin in combination with irinotecan in paediatric sarcomas. Due to the limited safety database and without a comparator arm, no firm conclusions on safety of eribulin in combination with irinotecan in paediatric patients can be drawn, however, no new safety concerns were identified.

The SmPC section 5.1 should include a brief description of the results of Study 213. It is noted that the MAH has already submitted a Type II variation (EMEA/H/C/002084/II/0060) to update the SmPC accordingly. Therefore, no further action is necessary based on the data from Study 213.

The PAM is considered

☒ **Fulfilled**

Annex. Line listing of all the studies included in the development program

Non-clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
Pediatric Preclinical Testing Program (PPTP) Stage 1 Testing for Eribulin	PPC-2012-02N	24 Apr 2012	Submitted on 19 Jun 2015 in Interim Compliance Check
Eribulin Stage 2 Results: Dose-Response, Additional Ewing Sarcoma Testing, and Pharmacokinetics	PPC-2013-01N	13 Dec 2013	Submitted on 19 Jun 2015 in Interim Compliance Check
Antitumor Activity of Eribulin Mesylate in Combination with Irinotecan Hydrochloride Trihydrate in KYM-1 Human Rhabdomyosarcoma Xenografts in Mice	M16010	30 Jan 2017	Submitted on 04 Apr 2018 in PIP modification request (EMEA-001261-PIP01-11-M05)

Clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 1 Study of Eribulin Mesylate (E7389, Ind #116,292), A Novel Microtubule Targeting Chemotherapeutic Agent In Children With Refractory Or Recurrent Solid Tumors (Excluding CNS), Including Lymphomas	E7389-A001-113 (ADVL1314)	28 Jan 2016	Submitted in July 2018 in the Deferral Annual Report submission. Also submitted as Article 46 submission in March 2019.
A Phase 2, multicenter, open-label study to assess safety and preliminary activity of eribulin mesylate in pediatric subjects with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) and Ewing sarcoma (EWS)	E7389-G000-223	22 Feb 2021	Submitted in Article 46 submission on 2nd August 2021.
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	E7389-G000-213	17 May 2021	Submitted in Article 46 submission on 15th November 2021.