14 October 2021
EMA/545362/2021
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/P46/025

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

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1. Introduction

On 2nd August 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.

2. Scientific discussion

2.1. Information on the development program

The MAH confirms that Study E7389-G000-223 is part of the clinical development program for eribulin and is Study 8 in the approved Paediatric Investigation Plan (EMEA-001261-PIP01-11-M06).

2.2. Information on the pharmaceutical formulation used in the study

Halaven 0.44 mg/mL solution for injection (marketed formulation)

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study E7389-G000-223 (Study 223) – A Phase 2, multicenter, open-label study to assess safety and preliminary activity of eribulin mesylate in paediatric subjects with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) and Ewing sarcoma (EWS)

The MAH suggests that the data submitted does not change the risk-benefit balance of eribulin and there is no regulatory consequence.

Eribulin is a microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. It was first approved in the EU in March 2011. It is currently approved for use in adult patients with previously treated locally advanced or metastatic breast cancer, or previously treated unresectable liposarcoma.

Study 223 is part of the paediatric investigation plan (PIP) for eribulin. The PIP includes one additional clinical study, Study 113, which has been finalised and was submitted in March 2019, in a P46 procedure. Study 113 was a Phase 1 study of eribulin in children with refractory or recurrent solid tumours (excluding central nervous system [CNS]), including lymphomas. Information from Study 113 was intended to help determine appropriate dosing in children with refractory or recurrent solid tumours, and to evaluate safety, toxicity and pharmacokinetics (PK). The maximum tolerated dose (MTD) for eribulin was concluded to be 1.4 mg/m^2. The best overall response was partial response (PR) for 1 subject and stable disease (SD) for 3 subjects. As it was an open, single-arm study investigating different doses in different histologies, and with few subjects included, no assessment of efficacy could be made, but it was concluded that the overall activity of eribulin in paediatric solid tumours seemed low.

2.3.2. Clinical study

Study E7389-G000-223 (Study 223):
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)

Description

Study 223 was an open-label, single-arm, multicentre study of eribulin mesylate in paediatric subjects with recurrent or refractory relapsed/refractory RMS, NRSTS or EWS, to assess preliminary activity in these three histologies. Eligible subjects ≥12 months and <18 years of age were eligible for enrolment.

Methods

Objective(s)

The primary aim of the study was to conduct a preliminary assessment of activity of eribulin mesylate in paediatric subjects with relapsed/refractory RMS, NRSTS or EWS to determine whether each cohort warrants further investigation.

Study design

The study consisted of 3 Phases: the Pre-study Phase, the Treatment Phase and the Follow-up Phase.

- The Pre-study Phase (Days -28 to -1) included assessments before the first dose of study drug to establish eligibility and baseline values.
- The Treatment Phase started on Day 1 of Cycle 1. Study treatment was discontinued if there was evidence of progressive disease or toxicity that required removal from treatment. Study treatment may otherwise have continued provided the subject had at least SD, met laboratory parameters defined in the eligibility criteria and did not meet any of the criteria for removal from protocol therapy or study discontinuation criteria. Subjects were followed for adverse events (AEs) for 28 days from the last dose of eribulin mesylate or until resolution of the events (for serious adverse events [SAEs], if resolution was unlikely, subjects were followed up until the event or sequelae stabilised).
- The Follow-Up period began immediately after the End-of-Treatment visit and until death or informed consent was withdrawn unless the study was terminated by the sponsor. Subjects were followed for survival approximately every 12 weeks for 1 year and annually thereafter. During the Follow-Up period, subjects who had discontinued study treatment without progression should have had tumour assessments every 6 to 12 weeks, at the investigator's discretion, from the date of last tumour assessment until disease progression was documented, death, or initiation of another anticancer therapy, whichever occurred first, unless the study was terminated by the sponsor. Follow-up data were required unless consent was withdrawn.

Study population

Paediatric subjects (age ≥12 months and <18 years) were eligible to take part in the study if they had histologically confirmed, relapsed or refractory RMS, NRSTS (Grade 2 or 3), or EWS and measurable disease meeting protocol-specified criteria, and with performance score ≥50 in Karnofsky or Lansky scale.

Subjects were not included in the study if they had >Grade 1 peripheral sensory neuropathy or >Grade 1 peripheral motor neuropathy (Modified ["Balis"] Pediatric Scale of Peripheral Neuropathies), protocol-specified cardiac pathology or CNS disease, or any serious concomitant illness that in the opinion of the investigator(s) could have affected the subject's safety or interfered with the study assessments.

Treatments

Study subjects were treated at the recommended Phase 2 dose (paediatric) of 1.4 mg/m^2, administered intravenously on Days 1 and 8 of a 21-day cycle.

Comment: The recommended dose for adults is 1.23 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle (Halaven SmPC).

Outcomes/endpoints

The primary objective of the study was:

- To conduct a preliminary assessment of activity of eribulin mesylate in paediatric subjects with relapsed/refractory RMS, NRSTS or EWS to determine whether each cohort warrants further investigation.

The secondary objectives of the study were:

- To evaluate the progression-free survival (PFS), using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, of eribulin mesylate in paediatric subjects with relapsed/refractory RMS, NRSTS, or EWS in all cohorts combined.
- To evaluate the safety and tolerability of eribulin in the paediatric subjects with relapsed/refractory RMS, NRSTS, or EWS in all cohorts combined.
- To evaluate the duration of response (DOR) of eribulin mesylate in paediatric subjects with relapsed/refractory RMS, NRSTS, or EWS.
- To evaluate the overall survival (OS) of paediatric subjects with relapsed/refractory RMS, NRSTS and EWS.

Statistical Methods

Primary endpoint:

Objective response: number of subjects achieving a best overall response of PR or complete response (CR), by up to 24 weeks after all subjects had completed response assessment. Response assessment was determined by investigators.

Results

Recruitment/ Number analysed

A total of 23 subjects were enrolled; 21 subjects were treated (8 subjects each in the RMS and NRSTS groups and 5 subjects in the EWS group) with eribulin mesylate at a dose of 1.4 mg/m^2.

All 21 subjects had discontinued treatment at the time of the data cutoff (22 Feb 2021); 19 subjects died, and 2 subjects were still in survival follow-up. The most frequent reasons for discontinuation were radiologic disease progression in 15 subjects (71.4%), clinical disease progression in 4 subjects (19.0%) and AEs in 2 subjects (9.5%).

All 21 treated subjects were included in the Full Analysis Set and Safety Analysis Set (primary analysis sets used for efficacy analysis and safety analysis sets, respectively).

Enrolment in the study was discontinued early due to lack of antitumor activity, following consultation with investigators and health authorities.

Baseline data

The median age of subjects was 13.0 years old (range: 2.0 to 17.0 years) and 13 of 21 subjects (61.9%) were between 12 and 17 years of age. Most subjects were male (14 [66.7%]) and white (11 [52.4%]) and a smaller proportion (5 [23.8%]) were of Black or African American descent. With the exception of 1 subject, all subjects had Lansky play score or Karnofsky performance status score of 70 or above at baseline.

Efficacy results

After treatment with eribulin mesylate, 6 subjects (28.6%) in total with RMS (n=3), NRSTS (n=1), or EWS (n=2) had a best overall response of SD and 12 (57.1%) subjects had a best overall response of progressive disease. No subjects achieved CR or PR (Table 1).

At the time of data cutoff (22 Feb 2021), the median PFS per RECIST 1.1 assessed by the investigator for the overall population was 1.41 months (95% CI: 0.76, 1.74). The Kaplan-Meier estimated PFS rate was 16.5% at 3 months and 0.0% at 6 months. At the time of data cutoff, 19 subjects (90.5%) had died. The median OS was 6.01 months (95% CI: 2.86, 8.51). The OS rate was 52.4% at 6 months, 16.3% at 12 months, and 10.9% at 18 and 24 months.

The aim of this study was to assess the preliminary efficacy of eribulin mesylate in paediatric subjects with RMS, EWS and NRSTS. After more than 15 subjects had been enrolled and treated, with at least 5 subjects treated per histology, no confirmed PR or CR was observed. Enrolment to the study was discontinued due to lack of antitumor activity, following consultation with investigators and health authorities.

Table 1. Summary of Tumour Response – Full Analysis Set

	RMS (N = 8)	NRSTS (N = 8)	EWS (N = 5)	Total (N = 21)
Best overall response (BOR)				
Complete response (CR),	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response (PR), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease (SD), n (%)	3 (37.5)	1 (12.5)	2 (40.0)	6 (28.6)
Progressive disease (PD), n (%)	3 (37.5)	6 (75.0)	3 (60.0)	12 (57.1)
Not evaluable[a], n (%)	2 (25.0)	1 (12.5)	0 (0.0)	3 (14.3)
Objective response (CR + PR), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
95% CI of Objective response rate[b]	(0.0, 36.9)	(0.0, 36.9)	(0.0, 52.2)	(0.0, 16.1)

Data cutoff date: 22 Feb 2021.
Assessments were performed by the investigator per RECIST 1.1.
Percentages are based on the number of randomized subjects in the relevant group.
EWS = Ewing sarcoma, NRSTS = non-rhabdomyosarcoma soft tissue sarcoma, RECIST = Response Evaluation Criteria in Solid Tumors, RMS = rhabdomyosarcoma.
a Subjects had clinical progression postbaseline and before the Week 6 tumor assessment.
b The 95% CI was calculated using exact (Clopper-Pearson) 2-sided 95% confidence limits.

Safety results

Exposure

At the time of the data cutoff date for this report (22 Feb 2021), the median overall duration of eribulin treatment was 6.0 weeks (range: 3.0 to 22.1 weeks). (Table 2).

Table 2. Study Treatment Extent of Exposure – Safety Analysis Set

Parameter	RMS (N = 8)	NRSTS (N = 8)	EWS (N = 5)	Total (N = 21)
Number of cycles received[a]				
n	8	8	5	21
Mean (SD)	2.9 (1.64)	1.9 (0.99)	3.0 (2.74)	2.5 (1.75)
Median	2.0	2.0	1.0	2.0
Q1, Q3	2.0, 4.0	1.0, 2.0	1.0, 6.0	1.0, 4.0
Min, Max	1, 6	1, 4	1, 6	1, 6
Number of cycles received[a], n (%)				
1 cycle	1 (12.5)	3 (37.5)	3 (60.0)	7 (33.3)
2 cycles	4 (50.0)	4 (50.0)	0 (0.0)	8 (38.1)
4 cycles	2 (25.0)	1 (12.5)	0 (0.0)	3 (14.3)
6 cycles	1 (12.5)	0 (0.0)	2 (40.0)	3 (14.3)
Duration of treatment (weeks)[b]				
n	8	8	5	21
Mean (SD)	9.07 (6.114)	5.80 (3.208)	9.83 (9.464)	8.01 (6.150)
Median	6.00	6.00	3.00	6.00
Q1, Q3	5.79, 12.00	3.00, 6.36	3.00, 18.00	3.00, 12.00
Min, Max	3.0, 22.0	3.0, 12.7	3.0, 22.1	3.0, 22.1
Total dose (mg/m^2) per subject				
n	8	8	5	21
Mean (SD)	7.55 (4.677)	5.09 (3.083)	7.48 (6.611)	6.59 (4.604)
Median	5.61	5.50	2.91	5.59
Q1, Q3	4.80, 11.27	2.76, 5.65	2.83, 11.84	2.91, 11.18
Min, Max	1.4, 15.6	1.4, 11.5	2.8, 17.0	1.4, 17.0
Dose intensity (mg/m^2/week) per subject[c]				
n	8	8	5	21
Mean (SD)	0.826 (0.1800)	0.852 (0.1632)	0.865 (0.1852)	0.845 (0.1667)
Median	0.922	0.903	0.943	0.912
Q1, Q3	0.697, 0.953	0.866, 0.919	0.930, 0.946	0.860, 0.946
Min, Max	0.48, 0.98	0.46, 0.98	0.53, 0.97	0.46, 0.98
Relative dose intensity (%) per subject[d]				
n	8	8	5	21
Mean (SD)	88.48 (19.288)	91.29 (17.489)	92.72 (19.855)	90.56 (17.867)
Median	98.78	96.74	101.02	97.74
Q1, Q3	74.76, 102.14	92.82, 98.51	99.70, 101.45	92.21, 101.45
Min, Max	51.5, 104.9	49.1, 105.1	57.3, 104.1	49.1, 105.1
Subjects with dose changes, n (%)	2 (25.0)	0 (0.0)	1 (20.0)	3 (14.3)

Data cutoff date: 22 Feb 2021.
Percentages are based on the number of randomized subjects in the relevant treatment group.
EWS = Ewing sarcoma, Max = maximum, Min = minimum, NRSTS = non-rhabdomyosarcoma soft tissue sarcoma, Q1 = first quartile, Q3 = third quartile, RMS = rhabdomyosarcoma.

a Subjects treated with at least one dose in Cycle X were counted as having received 'Cycle X'; the maximum cycle number for a subject was used as the number of cycles received for this subject.
b Duration of treatment (weeks) = (Date of first dose of last cycle + 21 - Date of first dose of study drug)/7.
c Dose intensity (mg/m^2/week) = Total dose (mg/m^2)/Duration of treatment (weeks).
d Relative dose intensity (%) = Dose intensity/Planned dose intensity × 100.

Adverse events

Treatment-emergent adverse events (TEAEs) were defined as those AEs that occurred (or worsened if present at Baseline) after the first dose of study drug through 28 days after the last dose of study drug.

All subjects reported at least 1 TEAE. The most commonly reported TEAEs (in 50% or more subjects) were neutrophil count decreased (71.4%), anaemia (66.7%) and white blood cell count decreased (61.9%). There were no reported TEAEs related to COVID-19 by the time of the data cutoff (22 Feb 2021).

Treatment-emergent adverse events of Grade 3 or higher were reported in 18 subjects (85.7%). The most commonly reported (in 20% or more subjects) Grade 3 or higher TEAEs were neutrophil count decreased (42.9%), white blood cell count decreased (38.1%) and anaemia (28.6%). Six of the 8 subjects who had TEAEs of Grade 3 or higher of white blood cell count decreased had also TEAEs of neutrophil count decreased.

Treatment-related adverse events

Treatment-related TEAEs were reported in 20 subjects (95.2%). Thirteen subjects (61.9%) had treatment-related Grade 3 or higher TEAEs; the most frequently reported treatment-related severe TEAEs (in 10% or more subjects) were neutrophil count decreased (38.1%), white blood cell count decreased (33.3%), anaemia (19.0%) and neutropenia (14.3%).

Serious adverse events and deaths

Overall, 11 subjects (52.4%) had at least 1 treatment-emergent SAE (fatal or nonfatal). Fatal treatment-emergent SAEs were reported in 3 subjects (14.3%) and were malignant neoplasm progression (2 subjects) and respiratory failure (1 subject); all 3 events were considered by the investigator to be related to disease progression.

The most frequent nonfatal treatment-emergent SAEs reported in 2 or more subjects were Grade 1 to 3 pyrexia (3 subjects, 14.3%) and 1 Grade 1 and 1 Grade 3 events of malignant pleural effusion (2 subjects, 9.5%).

Adverse events of special interest

The clinical overview specifically discussed AEs of alopecia, neutropenia, and peripheral neuropathy, as they can be noted with cytotoxic chemotherapy such as eribulin. In addition, events of QT prolongation were described.

- A total of 7 subjects (33.3%) had a TEAE of alopecia; 5 of these TEAEs were related to eribulin. Of the 7 TEAEs of alopecia, 6 were Grade 1 and 1 was Grade 2. By the time of the cutoff date for the primary analysis, 3 events of alopecia were resolving or resolved, 3 events did not resolve and for 1 event there was no reported outcome.
- A total of 17 subjects (81.0%) had both TEAEs of neutropenia and neutrophil count decreased of all grades. The majority of the events were related to eribulin and resolved or were resolving at the time of this report. Ten subjects (47.6%) had both TEAEs of neutropenia and neutrophil count decreased of Grade 3 or higher; 1 (4.8%) of those subjects had treatment-related, treatment-emergent SAEs of neutropenia which resolved after study drug interruption.
- Two subjects (9.5%) had treatment-related TEAEs of peripheral neuropathy: 1 subject had Grade 2 TEAEs of peripheral motor neuropathy and peripheral sensory neuropathy (both resolved) and 1 subject had a Grade 2 TEAE of peripheral sensory neuropathy (not resolved at the time of data cutoff). One subject (4.8%) had 2 events of Grade 3 neuralgia, a preferred term that belongs to Standardized Medical Dictionary for Regulatory Activities Query (narrow scope) of peripheral neuropathy. The events of severe neuralgia were assessed as related to

study treatment and resolved with dose reduction (first event) and eribulin discontinuation (second event).

- Six subjects (28.6%) had Grade 1 TEAEs of ECG QT prolongation; in 2 of these subjects the TEAEs were assessed as related to study treatment. All TEAEs of QT prolongation resolved. One subject had treatment-emergent SAEs of Grade 3 pericardial effusion, Grade 3 left ventricular dysfunction, and Grade 4 cardiac tamponade assessed as not related to eribulin, which resolved.

Adverse events leading to treatment discontinuation

In total, 3 subjects (14.3%) discontinued eribulin due to TEAEs; all of these subjects had at least 1 Grade 3 TEAE leading to discontinuation of eribulin. The TEAEs that led to study drug discontinuation were alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased (all in 1 subject), muscle weakness and neuralgia (in 1 subject each). All except 1 TEAE (a treatment-emergent SAE of neuralgia) leading to drug withdrawal were assessed as not related to eribulin.

2.3.3. Discussion on clinical aspects

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.*

None of the 21 subjects treated with eribulin monotherapy achieved PR or CR in Study 223. Due to the lack of responses, enrolment was discontinued early. The MAH's conclusion is agreed, i.e., that these results do not support further clinical development of eribulin monotherapy as a potential antitumor treatment strategy in paediatric subjects with relapsed/refractory RMS, NRSTS or EWS.

The safety profile of eribulin was consistent to that observed in adult subjects; no new safety signals were identified. The safety population is, however, small and the treatment duration was short. Based on this study, no firm conclusions can be drawn from a safety perspective, regarding the use of eribulin in a paediatric population.

The MAH suggests that the final report of this study does not warrant an update of the SmPC. However, according to the paediatric regulation (EC) No 1901/2006), results from paediatric studies,

even when there is lack of activity, should be included in the SmPC to provide guidance for the prescribers. Furthermore, the current text on deferral of studies with HALAVEN in one or more subsets of the paediatric population for the treatment of paediatric RMS and NRSTS should be amended to reflect finalisation of Study 223.

3. Rapporteur's overall conclusion and recommendation

The efficacy results of Study 223 do not support further clinical development of eribulin monotherapy in paediatric subjects with relapsed/refractory RMS, NRSTS or EWS. Due to the limited safety database, no conclusions on safety of eribulin monotherapy in paediatric patients can be drawn.

The SmPC should be updated with a brief description of the results of study 223, and the current texts on deferral of paediatric studies and lack of data should be updated to reflect finalisation of the study, as detailed below.

The PAM is considered

☒ Fulfilled:

In view of the available data regarding antitumour activity of eribulin in paediatric patients with relapsed/refractory RMS, NRSTS or EWS the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

- 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.

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

Nonclinical studies

Product Name: Halaven 0.44 mg/ml solution for injection Active substance: Eribulin

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

Clinical studies

Product Name: HALAVEN

Active substance: eribulin mesilate, eribulin

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.