2 STUDY SYNOPSIS

Name of Company: Eisai	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Halaven®	Referring to Module 5 of the Dossier	
Name of Active Ingredient: eribulin mesilate.	**Volume:** **Page:**	

Study Title

Phase II Study of E7389 Administered as an IV Infusion Day 1 and 8 Every 3 weeks in Pretreated Patients with Advanced and/or Metastatic Soft Tissue Sarcoma

Investigator(s)/ Site(s)

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Multicenter study (14 sites): Belgium (2), Denmark (2), Germany (5), Poland (1), and France (4).

Publication (Reference)

Schöffski P, Ray-Coquard IL, Cioffi A, Bui NB, Bauer S, Hartmann JT, et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. Lancet Oncol 2011 Oct;12(11):1045-52.

Study Period

13 Dec 2006 (first subject signed informed consent) to 28 Jun 2012 (last subject last visit + 30 days).

Phase of Development

Phase 2

Objective(s)

The primary objective of the study was to evaluate the therapeutic activity and safety of eribulin mesilate at a dose of 1.4 mg/m^2 on Days 1 and 8 every 3 weeks in subjects with advanced and/or metastatic soft tissue sarcoma (STS) who have relapsed following standard therapies.

Methodology

This was a Phase 2, multi-center, open-label, nonrandomized study to evaluate the efficacy and safety of eribulin mesilate in subjects with advanced STS who have failed standard chemotherapy.

The study enrolled subjects who had histologically confirmed and measurable (Response Evaluation Criteria In Solid Tumors [RECIST]) advanced or metastatic, or both, STS of the following histology: leiomyosarcoma (LMS), adipocytic (ADI), synovial sarcoma (SYN), or other types of sarcoma (OTH). There must have been evidence of objective progression within the last 6 months (RECIST), documented by disease measurements, without specific treatment since documentation of objective progression. Subjects must have had no more than one prior combination regimen or two single agent cytotoxic drugs for metastatic disease. Prior neoadjuvant chemotherapy or adjuvant chemotherapy, or both, were allowed. The subjects must have had a World Health Organization (WHO) performance status of one or less, adequate bone marrow, renal, liver, and cardiac function.

Subjects were registered at the European Organisation for Research and Treatment of Cancer (EORTC) Data Center after verification of the eligibility criteria and prior to the start of treatment. Treatment consisted of an intravenous bolus of eribulin mesilate (1.4 mg/m^2) over 2 to 5 minutes on Days 1 and 8 every 21 days. Subjects received the study drug until progression of the disease, unacceptable drug related events, intercurrent illness preventing further drug administration, or subject refusal. Subjects who demonstrated clinical benefit could continue treatment for as long as clinical benefit was sustained. The study included a screening visit, study assessments, and a post-treatment follow-up visit. During the treatment phase, the subjects underwent regular assessments for safety, clinical response, and pharmacokinetics (PK). Treatment activity was assessed at regular intervals and objective response was defined according to RECIST. The disease was assessed regularly until documented progression, and treatment side effects were assessed separately for each cycle of therapy.

The primary endpoint of the study was progression-free survival (PFS) at 12 weeks; therefore, the tumors were evaluated every 6 weeks during treatment, and at least 4 weeks after the first observation of a complete or partial response. Given the primary endpoint, the tumors were evaluated 12 weeks after the start of treatment in all subjects, even if study drug had been discontinued, unless progression was previously been documented.

Safety assessments included clinical examinations, assessments of adverse events (AEs), and laboratory tests; these were performed on Days 1, 8, and 15 during Cycles 1 and 2 and on Days 1 and 8 during Cycle 3. Electrocardiograms (ECGs) were also performed at the end of Cycle 2 and at study termination.

Number of Subjects (Planned and Enrolled)

Planned: A minimum of 68 subjects (17 in each of the four strata) and a maximum of 148 subjects (37 in each of the four strata) were planned for enrollment

Enrolled: 128 subjects were enrolled

Diagnosis and Main Criteria for Inclusion

Subjects with histologically proven advanced or metastatic malignant STS, or both, of high or intermediate grade, and one of the following histologies: LMS, ADI, SYN, or OTH. The disease had to be incurable by surgery or radiotherapy, and subjects must have received no more than one combination or two single agent chemotherapy regimens for advanced disease; (neo) adjuvant therapy was not counted towards this requirement.

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

Eribulin mesilate 1.4 mg/m^2 intravenous (i.v.) bolus given over 2 to 5 minutes on Days 1 and 8 every 21 days.
The batch numbers used during this study were: N0500442, N0600447, N0600942, N0700376, and N1100577.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

No reference therapy was used in this study.

Duration of Treatment

Subjects were treated until documented disease progression, unacceptable toxicity, or subject refusal. Subjects who demonstrated clinical benefit could have continued treatment for as long as clinical benefit was sustained.

Assessments

Efficacy

Efficacy was assessed using PFS at 12 weeks (RECIST). Tumors were evaluated every 6 weeks during treatment, and at least 4 weeks after the first observation of a complete or partial response. Given the primary endpoint of the study, tumors were evaluated 12 weeks after the start of treatment in all subjects (even if study drug had been discontinued, unless progression had been previously documented).

Efficacy was further assessed using the following secondary endpoints: overall PFS (assessed at the end of the study and defined as the time from date of first dose of study drug to the date of disease progression or date of death [whichever occurs first]), objective response rate (ORR) (defined by RECIST; documented and confirmed by two measurements taken at least 4 weeks apart), clinical response benefit (CRB) rate (defined by RECIST), time to onset of response (defined as time from first dose of study drug to date of objective response), duration of response (defined as time from achieving an objective response to time to first documented disease progression), and overall survival (OS) (defined as time from the date of first dose of study drug to date of death from any cause).

Pharmacokinetics

The PK data from this study was combined with PK data from seven Phase 1 studies and one Phase 2 study and was analyzed by a nonlinear mixed effect modeling approach. A three-compartment model with linear elimination was used as the starting point for analysis. Subject demographics and other subject parameters (e.g. laboratory parameters) were assessed as covariates for their effects on the PK of eribulin.

Pharmacodynamics

Population PK/pharmacodynamic (PD) model for changes in absolute neutrophil count from the same studies for which PK data were available was developed using a nonlinear mixed-effect model. A life cycle model for neutrophils, in which eribulin concentrations reduced the rated neutrophil production, served as the starting point for the analysis. Subject demographics and other subject parameters (e.g. laboratory parameters) were assessed as covariates which affected the eribulin neutropenia relationship. The relationship between predicted eribulin exposure versus the occurrence of Grade 3 or greater fatigue and neuropathy were explored graphically. Similarly the relationship between predicted eribulin exposure versus progression free survival at 12 weeks (PFS12), overall PFS and OS was explored graphically using Kaplan-Meier plots.

Pharmacogenomics/Pharmacogenetics

In the event of a positive clinical outcome in Step 1 (4 or more successes), a gene profiling analysis was to be performed and reported separately by the EORTC.

Safety

Safety assessments included toxic deaths, clinical examinations, assessments of adverse events and laboratory tests (hematology, serum chemistry, and urinalysis), were assessed prior to treatment and on Days 1, 8, and 15 during Cycles 1 and 2 and on Days 1 and 8 only from Cycle 3 onwards. Twelve-lead ECGs were performed prior to treatment, at the end of Cycle 2 and at study termination. National cancer institute's (NCI) common terminology criteria for adverse events (CTCAE) Version 3.0 was used for evaluation of side-effects.

Statistical Methods

The study was conducted in four different strata: LMS, ADI (liposarcoma dedifferentiated, myxoid/round cell, pleomorphic, mixed-type, not otherwise specified), SYN, and OTH.

The Simon two-stage design was separately applied to each stratum: 17 or 37 subjects were to be registered in each stratum, according to the number of responses observed in the first 17 subjects: if three or fewer successes (where a

"success" was defined as a subject being progression-free [stable disease or complete or partial response] at Week 12) were observed in a stratum, the study was to be stopped in this stratum with the conclusion that the study drug should not be further investigated in these tumor types, otherwise, subject accrual was continued until 37 subjects had been recruited and had started study drug.

For AEs, the worst grade of each event was tabulated, in each stratum. The distribution across strata was also provided. Population PK analysis was used to characterize the PK profile of eribulin mesilate. A nonlinear mixed effects modeling procedure, as implemented in the NONMEM program, was used to conduct the population PK analysis.

PFS at 12 weeks was summarized using a binary rate and presented as a percentage.

Overall PFS, overall survival, time to onset of response and duration of response were each summarised using Kaplan-Meier estimates. ORR and CRB were summarised as rates and presented as percentages. Confidence intervals (CI) were also calculated for each relevant summary.

No hypothesis testing was performed.

The following analysis sets were defined for this study: All Enrolled, Safety Analysis Set, Full Analysis Set (FAS), and Efficacy Evaluable Set (EES). The All Enrolled Set was used for the disposition tables, the Full Analysis Set was used for baseline outputs, the EES was used for efficacy outputs, the Safety Analysis Set was used for the safety outputs, and the FAS was used for all efficacy endpoints. Efficacy tables were produced using the EES and repeated on the FAS for selected endpoints, as a supportive analysis.

A cutoff date of 28 Jun 2012 was used for data in this study. This date was 30 days after the last subject discontinued treatment (28 May 2012).

Results
Subject Disposition/Analysis Sets

A total of 128 subjects were enrolled into the study and were allocated into four different subject strata following histopathology review (ADI, LMS, SYN, and OTH). Of these, 127 subjects were evaluable for safety (37, 40, 19, and 31 subjects were included in each of the ADI, LMS, SYN, and OTH strata, respectively), and 115 subjects were evaluable for efficacy (32, 38, 19, and 26 subjects were included in each of the ADI, LMS, SYN, and OTH strata, respectively). Following the reassessment of study eligibility by the central review panel, 12 subjects who were previously assessed by local pathologist's diagnosis on study entry as eligible for treatment (and began treatment) were then assessed as ineligible (5 subjects in the ADI stratum, 2 subjects in the LMS stratum, and 5 subjects in the OTH stratum). The most frequent reasons for ineligibility, as determined by the central review, were histology (tumor type) and no documented objective progression at trial entry each with 4 subjects. One subject developed brain metastases before the intended start of protocol treatment and therefore did not begin treatment with eribulin.

Efficacy

The primary efficacy endpoint was PFS as assessed 12 weeks after the start of treatment in the EES and showed that the four STS variants responded differently to treatment with eribulin with PFS at 12 weeks in 15 subjects [47%] in the ADI stratum, 12 subjects [32%] in the LMS stratum, 4 subjects (21%) in the SYN stratum, and 5 (19%) subjects in the OTH stratum.

Overall PFS was a secondary endpoint and was assessed at the end of the study. At last follow up, only 1 subject (in the LMS stratum) in the EES population was observed to be progression-free. The median (95% confidence interval) PFS time was similar for each of the four strata (82 [44, 175] days, 88 [69, 114] days, 81 [43, 101] days, and 72 [42, 87] days for the ADI, LMS, SYN, and OTH strata, respectively).

The secondary efficacy endpoint of ORR to therapy as defined by RECIST was calculated as complete response (CR) + partial response (PR). One subject in the EES (ADI stratum) was observed with a CR at Week 12; one

subject in each of the ADI, SYN, and OTH strata experienced a PR. There was little difference among the strata for the ORR (3%, 5%, 5%, and 4% for the ADI, LMS, SYN, and OTH strata, respectively).

The secondary efficacy endpoint of CRB rate was determined by CR + PR + stable disease (SD). The majority of subjects in the ADI and LMS strata had a best overall response (BOR) of SD (56% and 53% for the ADI and LMS strata, respectively) and for the SYN and OTH strata, 42% of subjects had a BOR of SD. A slightly higher proportion of subjects in the ADI and LMS strata achieved CRB compared with the SYN and OTH strata (59% and 58% versus 47% and 46%).

The secondary efficacy endpoints of time to onset of response and duration of response were only calculated for subjects who had a BOR of CR or PR; this included 5 subjects (4%) overall. The median (95% CI) time to onset of response was 86 (42, 211) days and the median (95% CI) duration of response was 102 (85, 418) days. Given the small number of subjects achieving these responses, no comparison can be made among the strata.

Overall survival was also assessed as a secondary endpoint. A total of 11 subjects (10%) remained alive at the end of the study (4 subjects [13%], 5 subjects [13%], 1 subject [5%], and 1 subject [4%] in the ADI, LMS, SYN, and OTH strata, respectively). For overall survival, in the EES, the best outcomes were reported in subjects in the LMS stratum (median [95% CI]: 466 [392, 697] days) followed by the ADI stratum (363 [234, 495] days). This compared with a lesser duration of 293 (170, 371) days for the SYN stratum and 204 (149, 312) days for the OTH stratum. The overall survival rate calculated using the Kaplan-Meier estimate showed overall survival of 91% at 3 months (81%, 85%, 100%, and 100% in the ADI, OTH, LMS, and SYN strata, respectively). By 12 months the overall survival for the EES was 50% (31%, 39%, 50%, and 68% in the OTH, SYN, ADI, and LMS strata, respectively).

For all endpoints (primary and secondary), results obtained when the analyses were repeated using the FAS were similar to results from the EES population.

Pharmacokinetics, Pharmacodynamics Pharmacogenomics/Pharmacogenetics

The PK of eribulin was described by a three-compartment model parameterized in terms of clearance (CL), volume of central compartment (V1), inter-compartment clearance between V1 and V2 (Q1), volume of peripheral compartment (V2), inter-compartment clearance between V2 and V3 (Q2), and volume of second peripheral compartment (V3) with allometric scaling accounting for body size effect on each of the PK parameters. The effects of albumin, alkaline phosphatase, and bilirubin on eribulin CL were found to be statistically significant with CL increasing significantly with albumin levels (power = 0.607), and decreasing significantly with alkaline phosphatase levels (power = -0.178) and total bilirubin levels (power = -0.170). No other covariates significantly affected the PK of eribulin, including age, gender, and WHO performance status. No clinically relevant trends between the subject covariates – gender, age, WHO performance status score, and tumor type – with individual eribulin exposure (area under the concentration-time curve [AUC]) were apparent based on graphical evaluation.

Eribulin-induced changes in neutrophil proliferation were described by a semi-physiological model for hematological toxicity in which eribulin decreased neutrophil proliferation. The population model parameter estimates for baseline neutrophil measurements (BASE), mean neutrophil transition time (MTT), neutrophil proliferation feedback parameter (γ) and the drug effect parameter on neutrophil proliferation (SLOPE) were 4.24 IU/L, 107 hours, 0.206, and 0.0358 mL/ng, respectively with moderate IIV (inter-occasion variability).

Albumin levels, granulocyte colony stimulating factor (G-CSF) co-administration, ALP and aspartate aminotransferase (AST) levels significantly affected neutrophil proliferation in the presence of eribulin. Baseline neutrophils declined with increasing plasma albumin levels, (power = -0.547). MTT for neutrophil maturation, which is a reflection of mean time taken from progenitor cells to matured cell in plasma, was approximately 19% faster in subjects co-administered with G-CSF. This effect was due to G-CSF stimulating bone marrow to produce and release granulocytes into the circulation. Eribulin effect (SLOPE) on inhibition of neutrophil proliferation increased slightly with increasing AST levels (power = 0.186) and decreased slightly with increasing ALP levels (power = -0.149). Inhibition of neutrophil proliferation by eribulin was 35 % greater in those subjects receiving G-CSF medication. The greater inhibition of proliferation with G-CSF administration reflected that subjects

receiving G-CSF were experiencing lower neutrophil maturation levels.

Based on graphical analysis, subjects experiencing Grade ≥3 fatigue were exposed to higher levels of eribulin on average for each dose administered (AUC_{av}) and also as a whole during the study.

No relationship between eribulin exposure and or overall PFS was observed (based on graphical analysis of Kaplan-Meier plots). OS was longer in subjects with above median eribulin area under the concentration-time curve, per average dose level (AUC_{av}) (>817.4 ng.h/mL) however this was mostly the case when little data are available (>125 weeks) and this observation should be viewed with caution. No relationship between eribulin AUC_{av} versus BOR could be detected.

Safety

Safety analyses were based on all 127 subjects who started treatment with eribulin. The median duration of treatment was 64 days and the median number of cycles received was 4.0. Across the strata groups, there was a difference in exposure duration. Median duration of treatment was 71, 61, 71, and 36 days for the ADI, LMS, SYN, and OTH strata, respectively. At all time points during the study, the most frequent reason for stopping treatment was disease progression/relapse/death due to progression, the incidence of which was balanced across the four strata.

Overall, treatment-emergent adverse events (TEAEs) were reported in 124 (97.6%) subjects. The incidence of TEAEs was similar in all strata. The most common TEAEs (occurring in ≥40% subjects) were fatigue, peripheral sensory neuropathy, alopecia, and nausea in the ADI stratum; fatigue, alopecia, and peripheral sensory neuropathy in the LMS stratum; fatigue, tumor pain, alopecia, dyspnea, and nausea in the SYN stratum; and fatigue and tumor pain in the OTH stratum. Some differences were observed among the four strata in the incidence of these common AEs. The incidence of peripheral sensory neuropathy was lowest in the OTH stratum (6 [19.4%] subjects) compared with the ADI, LMS, and SYN strata (17 [45.9%], 16 [40.0%], and 7 [36.8] subjects, respectively). Tumor pain occurred more frequently in the SYN and OTH strata (11 [57.9%] and 16 [51.6%] subjects, respectively) compared with the ADI and LMS strata (10 [27.0%] and 11 [27.5%] subjects, respectively). The incidence of dyspnea was highest in the SYN stratum (10 [52.6%] subjects compared with 10 [27.0%], 11 [27.5%], and 10 [32.3%] subjects in the ADI, LMS, and OTH strata, respectively. The incidence of alopecia ranged from 11 (35.5%) subjects in the OTH stratum to 16 (43.2%) subjects in the ADI stratum, 10 (52.6%) subjects in the SYN stratum, and 24 (60.0%) subjects in the LMS stratum.

Overall, 51% of subjects had at least one TEAE of Grade 3 or 4. In general, the incidence of Grade 3 or 4 TEAEs was similar in all four strata although subjects in the OTH stratum showed a higher incidence of Grade 3 or 4 tumor pain (7 [22.6%] subjects) compared with subjects in the ADI, LMS, and SYN strata (1 [2.7%] subject, no subjects, and 1 [5.3%] subject, respectively).

Overall, 114 (89.8%) subjects experienced TEAEs that were considered by the investigator to be related (i.e., possibly or probably related) to study drug and the incidence was similar across the four strata. In the overall population, the most common treatment related TEAEs (occurring in ≥30% subjects) were fatigue, nausea, peripheral sensory neuropathy, and alopecia.

Overall, there were TEAEs that led to death in 3 subjects during the study, 1 subject in the ADI stratum (malignant pleural effusion) and 2 subjects in the LMS stratum (1 subject with general physical health deterioration and 1 subject with cerebral ischemia).

Overall, SAEs were reported in 47 (37.0%) subjects. The incidence of serious adverse events (SAEs) was similar across all four strata (37.8%, 30.0%, 36.8%, and 45.2% of subjects in the ADI, LMS, SYN, and OTH strata, respectively). The most common SAEs (all occurring in 4 [3.1%] subjects overall) were febrile neutropenia, general physical health deterioration, pyrexia, and tumor pain. Treatment related SAEs were reported in 14 (11.0%) subjects; the most common were febrile neutropenia (in 4 subjects overall), and neutropenia, pneumonia, and pyrexia (each in 2 subjects overall).

A total of 11 subjects were recorded with “adverse event” as the primary reason for discontinuation from treatment.

This included 3 subjects in each of the ADI, LMS, and OTH strata and 2 subjects in the SYN stratum.

Shifts from either Grade 0, Grade 1, or Grade 2 parameters to either Grade 3 or Grade 4 by Last On-Treatment assessment (or value) were observed for more subjects for the parameters of lymphocytes (10 subjects), neutrophils (17 subjects), and white blood cells (WBCs) (12 subjects) compared with either hemoglobin or platelets. For neutrophils and WBCs, more shifts to Grade 3 and Grade 4 were observed at Day 8 and Day 15 (compared with Day 1) and mainly restricted to the first couple of cycles. There were no notable trends in shifts from Grade 0, Grade 1, or Grade 2 parameters to either Grade 3 or Grade 4 by Last On-Treatment visit for any of the clinical chemistry parameters. Markedly abnormal treatment-emergent Grade 3 or Grade 4 hematology laboratory test results were reported for neutrophils (66 subjects [52.0%]), WBCs (44 subjects [34.6%]), lymphocytes (28 subjects [22.0%]), and hemoglobin (6 subjects [4.7%]); there were no consistent differences in percentages of Grade 3 and Grade 4 events among the four strata. For clinical chemistry parameters, treatment-emergent Grade 3 and Grade 4 markedly abnormal laboratory test results were recorded for phosphorus (19 subjects [17.0%]), potassium (7 subjects [5.5%]), sodium (7 subjects [5.5%]), alanine aminotransferase (ALT) (5 subjects [4.0%]), albumin (4 subjects [3.2%]), calcium (4 subjects [3.2%]), ALP (1 subject [0.8%]), and bilirubin (1 subject [0.8%]); there were no consistent differences in percentages of Grade 3 and Grade 4 events among the four strata. Nothing of note was observed for any urinalysis parameter over time among the strata.

There were no consistent changes in vital signs during the study, other than a possible trend for a reduction in weight from baseline.

No abnormal, clinically significant ECG data were recorded during the study. There was very little change in WHO performance status over the course of the study and most subjects remained Grade 0 or Grade 1 throughout.

Conclusions

The data indicate that eribulin is a safe and potentially active drug in pretreated subjects with soft-tissue sarcoma as evidenced by the ORR observed in all four variants (ADI 3%, LMS 5%, SYN 5%, and OTH 4%).

The main findings of the study are:

- The study primary endpoint showed a PFS rate at 12 weeks of 47% for ADI, 32% for LMS, 21% for SYN, and 19% for OTH.
- All four variants met the pre-specified primary efficacy criteria (PFS at 12 weeks) during the Simon's first stage design. Whereas ADI and LMS satisfied the second stage threshold, the SYN and OTH variants did not complete the recruitment of the second stage based on a projection made from the activity achieved at 12 weeks, thus, making difficult to raise conclusions concerning these two sarcoma variants.
- Overall survival analysis, a secondary endpoint, shows a greater proportion of subjects in the ADI and LMS strata remained alive at the end of the study (13% in each), compared with subjects in the SYN and OTH strata (5% and 4%, respectively).
- The Grade 3 to 4 hematological toxicity was manageable and was demonstrated to be fully in line with the known safety profile of eribulin.
- Compared with the global safety data base of eribulin, the slightly increased frequency of febrile neutropenia can be understood in the context of existing additional circumstances that may have contributed to the potentiation of the expected bone marrow toxicity of eribulin.
- The Grade 3 to 4 nonhematological toxicity events were relatively infrequent.
- The incidence of TEAEs was similar in all strata and the most frequently reported TEAEs (occurring in

≥40% subjects) were fatigue and alopecia.

- Although the safety profile was broadly similar, there were some small differences between strata, with more incidence of peripheral sensory neuropathy within ADI and LMS strata, and tumor pain within SYN and OTH. Fatigue was uniformly present across all strata but the proportion compared favorably with that reported with any other standard chemotherapy treatment.

- In the very heterogeneous OTH stratum, drug activity was observed in some subtypes commonly believed to be refractory to chemotherapy, and this characteristic might have played some role in its apparently modest clinical outcome compared with more homogeneous variants.

- Taken together, that the Grade 3 to 4 hematological toxicity was manageable and in line with the known safety profile of eribulin, and the Grade 3 to 4 nonhematological toxicity events were infrequent, and the incidence of fatigue compared favorably with that reported for other standard chemotherapy treatments indicate that eribulin may have a role in advanced or metastatic STS.

Date of Report

24 June 2013