2 STUDY SYNOPSIS

Name of Company: Eisai Inc.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Eribulin mesilate, intravenous solution	Referring to Module 5 of the Dossier	
Name of Active Ingredient: Eribulin mesilate	Volume: Page:	

Study Title

A Randomized, Open-label, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Eribulin with Dacarbazine in Subjects with Soft Tissue Sarcoma.

Investigators/Sites

Name: Professor Dr. Patrick Schöffski, MPH (principal investigator).

Multicenter: Approximately 130 global sites (refer to Appendix 16.1.4 for the list of investigators and sites)

Publication (Reference)

None

Study Period

March 2011 to March 2015

Phase of Development

Phase 3

Objective(s)

Primary:

- To compare overall survival (OS) in subjects with advanced soft tissue sarcoma ([STS], one of two subtypes: adipocytic [ADI] or leiomyosarcoma [LMS]) when treated with eribulin (Arm A) or dacarbazine (Arm B).

Secondary:

- To compare progression-free survival (PFS) between Arm A and Arm B.
- To compare progression-free rate at Week 12 (PFR_{12wks}) between Arm A and Arm B.
- To compare the clinical benefit rate (CBR) (complete response [CR], partial response [PR], or durable stable disease [dSD]: duration of stable disease [SD] ≥ 11 weeks) between Arm A and Arm B.
- To compare the safety and tolerability between Arm A and Arm B.
- To characterize the population pharmacokinetics (PK) of eribulin in subjects with STS.

Exploratory:

- To compare:
  - Objective response rate ([ORR] CR or PR), between Arm A and Arm B.
  - Disease control rate ([DCR], CR, or PR, or stable disease [SD]), dSD rate, between Arm A and Arm B.
- To explore the relationship between exposure to eribulin and pharmacodynamic biomarkers and efficacy.
- To explore the relationship between exposure to eribulin and adverse events.
- To investigate and identify blood and tumor biomarkers which can be correlated with safety and efficacy endpoints.

- To compare quality of life (QoL) scores between Arm A and Arm B.

Methodology

This was a randomized, open-label, multicenter, Phase 3 study to compare the efficacy and safety of eribulin with dacarbazine in subjects with advanced (locally recurrent, locally advanced and/or metastatic) STS (one of two subtypes: adipocytic sarcoma [ADI] or leiomyosarcoma [LMS]) not amenable to surgery and/or radiotherapy, who had disease progression within 6 months prior to randomization following at least two standard systemic regimens for advanced STS, one of which must had been an anthracycline (unless contraindicated).

Subjects had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, with the modification that chest X-ray could not be used for assessment of chest lesions.

Subjects were randomly assigned in a 1:1 ratio to receive one of 2 treatment arms: Arm A (Eribulin mesilate) or Arm B (Dacarbazine) on a 21-day treatment cycle. Randomized subjects were stratified by geographic regions (Region 1: USA and Canada; or Region 2: Western Europe, Australia and Israel; or Region 3: Eastern Europe, Latin America, and Asia), tumor histology (ADI or LMS), and number of prior regimens for advanced STS (2 or >2 prior regimens).

The study was conducted in 3 phases: a Prerandomization Phase, a Randomization Phase, and an Extension Phase. The Randomization and the Extension Phase consisted each of 2 periods: Treatment Cycles and Follow-up.

- The **Prerandomization Phase** had 2 periods: Screening and Baseline. The purpose of the **Screening Period** was to obtain subject informed consent and to determine protocol eligibility. The purpose of the **Baseline Period** was to confirm protocol eligibility and proceed subject to randomization.
- The **Randomization Phase**:
  - The **Treatment Cycles** began with the first dose of study treatment until completion of the Off-treatment Visit. Tumor assessments were performed every 6 weeks from the date of randomization for the first 12 weeks and every 9 weeks thereafter, or sooner, if clinically indicated, until disease progression was confirmed. This schedule for tumor assessments was maintained irrespective of treatment delays.
  - The **Follow-up Period** began immediately after the Off-treatment Visit and continued as long as the subject was alive. Survival follow-up was conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Subjects who discontinued study treatment were treated according to the prevailing local standard-of-care.

The Randomization Phase ended at the time of data cut-off for the primary analysis, when the target numbers of events (estimated to be 353 deaths) were observed. All subjects who were still on the Treatment Cycle or in the survival Follow-up Period of the Randomization Phase at the time of data cut-off, were entered the in the Extension Phase.

- The **Extension Phase**:
  - The **Treatment Cycles** included all subjects who had received study treatment at the end of the Randomization Phase (ie, after the number of targeted events were observed). Subjects received the same treatment (Arm A or Arm B) that they had received in the Randomization Phase. Following completion of the Treatment Cycle in the Randomization Phase, subjects entered the next Treatment Cycle in the Extension Phase (for example, after completing Cycle 1 of the Randomization Phase entered Cycle 2 of the Extension Phase). Tumor assessments were performed according to the same schedule as during the Treatment Cycles of the Randomization Phase.

- The **Follow-up Period** began immediately after the Off-treatment Visit and continued as long as the subject was alive. Subjects who were in the survival Follow-up Period at the end of the Randomization Phase continued survival follow-up approximately every 12 weeks in the Extension Phase unless they withdrew consent or the survival follow-up was terminated by the Sponsor.

Subjects who discontinued study treatment without disease progression continued to undergo tumor assessment according to the same schedule as during the Treatment Cycles, or sooner, if clinically indicated, until disease progression was confirmed, or before another anticancer therapy was initiated (if more than 6 weeks had elapsed since the last tumor assessment).

Subjects remained on study treatment until progression of disease (PD), development of unacceptable toxicity, withdrawal of consent or Sponsor discontinuation of the study.

Termination of the survival follow-up during the Extension Phase (after the completion of the primary analysis and when all subjects discontinued study treatment) was at the discretion of the Sponsor.

Number of Subjects (Planned and Enrolled)

Planned: Approximately 450 subjects were planned to be enrolled.

Enrolled: A total of 452 subjects were enrolled and randomized.

Treated: 450 subjects received study drug (226 to Arm A and 224 to Arm B)

Diagnosis and Main Criteria for Inclusion

Men and women at least 18 years of age with a histologically confirmed diagnosis of soft tissue sarcoma, documented evidence of advanced (locally recurrent, locally advanced or metastatic) adipocytic (including dedifferentiated, myxoid, round cell and pleomorphic subtypes) or leiomyosarcoma, incurable by surgery or radiotherapy, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or 2 were eligible. Other main inclusion criteria included radiographic evidence of disease progression on or after the last anti-cancer therapy within 6 months prior to randomization, subjects should have received at least two standard systemic regimens for STS one of which must have included an anthracycline (unless contraindicated), adequate renal bone marrow, blood coagulation and liver function, and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

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

Test Product: Eribulin (Arm A) was supplied in glass vials containing 1.0 mg eribulin mesilate in 2.0 mL of clear, colorless, and sterile solution.

Dose and mode of administration: 1.4 mg/m^2 intravenous (IV) bolus infusion over 2-5 minutes on Days 1 and 8 of every cycle, where the duration of each cycle is 21 days.

Dose reduction and interruption for subjects who experienced eribulin related toxicity were in accordance with eribulin dose reduction and interruption instructions.

Batch Number(s): N0600942, N0700376, N0900414, N1101538, N1200473. In addition, 1 batch of eribulin was supplied commercially (batch 103893).

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

Comparator: Dacarbazine (Arm B)

Dose and mode of administration: 850 mg/m^2 or 1,000 mg/m^2 or 1,200 mg/m^2 (selected by the PI or designee) IV infusion over 15-30 minutes (or up to 60 minutes per institutional guidelines) on Day 1 of every cycle, where the duration of each cycle is 21 days.

Dose reduction and interruption for subjects who experienced dacarbazine related toxicity was in accordance with the dacarbazine prescribing information.

Batch Number(s):

100 mg vial	E100261B, I100580B, K100639B
200 mg vial	A110010B, C110195A, E100262C, F110401A, G120968C, H100445C, I100579B
500 mg vial	C100161H, C110079A, E130380A, G100376B, G100395D, M100772A

In addition, batches 26488, D110199F, and I110676B were hospital supplies, and the vial size was not recorded.

Duration of Treatment

The duration of treatment for each subject was estimated to be approximately 2 months for the Randomization and 2 months for the Extension.

Treatment continued until disease progression, development of unacceptable toxicity or withdrawal of consent. The Randomization Phase ended at the time of data cut-off for the primary analysis, and all subjects still on study treatment at data cut-off continued to receive the same study treatment in the Extension Phase.

Assessments

Efficacy

Tumor Response Assessment

Tumor assessment was carried out on all subjects at Screening and during the Randomization and Extension Phases. During the Randomization Phase every 6 weeks from the date of randomization for the first 12 weeks, and every 9 weeks thereafter or sooner, if clinically indicated, until disease progression was confirmed. During the Extension Phase, subjects underwent tumor assessments according to the same schedule as during the Treatment Cycles of the Randomization Phase, or sooner if clinically indicated, until disease progression was confirmed.

The schedules for tumor assessment during the Randomization and Extension Phases were maintained irrespective of treatment delays. Subjects who discontinued study treatment without disease progression continued to undergo tumor assessment according to the same schedule as during the Treatment Cycles, or sooner, if clinically indicated, until disease progression was confirmed, or before another anti-cancer therapy is initiated (if more than 6 weeks have elapsed since the last tumor assessment).

Tumor response was evaluated using RECIST 1.1, with the modification that chest X-ray was not to be used for assessment of chest lesions. All scans and photographs performed during the study were sent to the imaging core lab (ICL) designated by the Sponsor for archival and potential independent radiologic review.

Pharmacokinetics

Plasma concentrations of eribulin were measured in subjects that had available PK samples in Arm A. A population PK model of eribulin was developed using non-linear mixed effect modeling. The model was parameterized in terms of clearance and volume of distribution.

Pharmacodynamics

Pharmacodynamic (PD) samples were collected on all subjects in both Arm A and Arm B, unless it was explicitly prohibited or required to be optional by country or regional regulations or IRB/EC requirements. The Sponsor was made aware of such regulations at the time of study start-up.
Pre-study tumor samples were collected at Screening from all randomized subjects to explore tumor characteristics that may have correlated with the outcomes of the study.

Blood samples for extraction of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and pharmacodynamics for retrospective analysis of candidate biomarkers from completed, ongoing or future studies were collected during Pre-randomization and Randomization Phases.

Safety

Safety was assessed by monitoring and recording of all adverse events (AE) including all CTCAE v4.0 grades (both increasing and decreasing severity) and serious adverse events (SAE), regular monitoring of hematology, clinical chemistry, urinalysis, regular measurement of vital signs, electrocardiograms (ECGs), and physical examinations.

Other

Pharmacokinetic/pharmacodynamic (PK/PD) relationships, ie, dose and/or exposure effect relationships were explored for the effects of eribulin on tumor responses as determined by RECIST 1.1 (CR, PR and SD), PFS and OS, as well as adverse events (AEs)/dose reductions and interrelationships. Exploratory/graphical analysis was conducted for PK/PD evaluations, and followed by model-based analysis.

Bioanalytical Methods

Eribulin was quantified using a validated liquid chromatography-tandem mass spectrometry method.

Statistical Methods

Primary Efficacy Endpoint:

- OS measured from the date of randomization until date of death from any cause.

Secondary Efficacy Endpoints:

- PFS, defined as the time from the date of randomization to the date of first documentation of disease progression, or date of death (whichever occurs first).
- PFR_{12wks}, defined as the proportion of subjects alive and progression-free at 12 weeks from the date of randomization.
- CBR, defined as the proportion of subjects who had best overall response of CR or PR or dSD (duration $\geq$ 11 weeks).
- Safety endpoints included AEs according to CTCAE v4.0 grades and serious AEs, hematology and clinical chemistry, urinalysis, regular measurement of vital signs, 12-lead ECGs and performance of physical examinations.
- Population PK profile of eribulin in the subjects with STS.

Exploratory Endpoints

- ORR, the proportion of subjects who had overall response of CR or PR.
- DCR, the proportion of subjects who had best overall response of CR, or PR, or SD.
- dSD, defined as the proportion of subjects who had the duration of SD $\geq$11 weeks.
- QoL scores, measured using the QLQ C30 and EQ-5D questionnaires.
- The following exploratory PK/PD endpoints:
  - Relationship between exposure to eribulin and pharmacodynamic biomarkers and efficacy.
  - Relationship between exposure to eribulin and AEs.
  - Blood and tumor biomarkers which may be correlated with safety and efficacy endpoints.

Analysis Sets

- Full Analysis Set (Intent-to-treat Analysis Set) included all subjects who were randomized. This was the primary analysis set for all efficacy endpoints.
- Per Protocol Analysis Set included those subjects who received at least one dose of study treatment and had no major protocol violations. This was the secondary analysis set for all efficacy evaluations.
- Safety Analysis Set included all subjects who were randomized, received at least one dose of the study treatment, and had at least one post-baseline safety evaluation. This was the analysis set for all safety evaluations.
- Pharmacokinetic Analysis Set included all subjects with at least one quantifiable eribulin concentration with a documented related dosing history.
- Pharmacodynamic Analysis Set included all subjects who received at least one dose of study treatment and have available PD data.

Efficacy Analyses

Analysis of Primary Efficacy Endpoint:

The OS was compared between the two treatment arms using a two-sided stratified log rank test at a nominal significance level of 0.0455 (adjusted for the interim analysis). The test was stratified by histology, geographic region and number of prior regimens for advanced STS: this is the primary analysis that was performed when the target number of events (~353 deaths) was observed.

OS was measured from the date of randomization until date of death from any cause. In absence of confirmation of death, the subjects were censored either at the date that the subject was last known to be alive or the date of study cut-off, whichever came earlier.

The median OS and the cumulative probability of OS at selected time points were calculated for each treatment arm and presented with 2-sided 95% Confidence Interval (CI). The selected time points were dependent on the OS times that were observed during the study and are specified in the statistical analysis plan (SAP).

Greenwood's formula was used for the standard error of the Kaplan-Meier estimate in the calculation of these confidence limits. Kaplan-Meier survival probabilities for each arm were plotted over time.

The treatment effect was estimated by fitting a Cox Proportional Hazards model to the OS times including treatment arm as a factor and histology, geographic region and number of prior regimens for advanced STS as strata. From this model, the hazard ratio of eribulin to dacarbazine was estimated and presented with a 2-sided 95% CIs.

An additional exploratory Cox regression model was fitted in which the hazard ratio was stratified by histology and geographic region while other variables of interest were fitted as covariates.

These analyses were performed on the Full Analysis Set as primary analysis.

Analyses of Secondary Efficacy Endpoints:

1. Progression-Free Survival

The statistical significance of the difference in PFS (as determined by the tumor response evaluation as determined by the PI or designee) between eribulin and dacarbazine was evaluated using the log rank test, stratified by histology, geographic region and number of prior regimens for advanced STS, tested at an alpha level of 0.05. The corresponding estimate of hazard ratio calculated from a stratified Cox-proportional hazards model was presented with a 2-sided 95% CI. Median PFS time and the cumulative probability of PFS at 3 and 6 months were calculated for each treatment arm, and presented with corresponding 2-sided 95% CIs.

2. Progression-Free Rate at Week 12 (PFR_{12wks})

PFR_{12wks} was estimated by treatment arm based on the tumor response evaluation performed by the PI or designee according to RECIST 1.1. The statistical significance of the difference in PFR_{12wks} between treatment arms was calculated using the Cochran-Mantel-Haenszel (CMH) chi-square test with histology, geographic region, and number of prior regimens for advanced STS as strata, tested at an alpha level of 0.05. A 95% 2-sided CI of the difference in PFR_{12wks} was constructed as well as similar CIs for the rate within treatment arm. Subjects were considered as "successes" if one radiological evaluation performed during Week 12 after randomization indicated a "SD" or a "response". All other cases were considered as failures (including subjects who have progressed or died before Week 12 evaluation, and subjects with an unknown disease status at Week 12).

3. Clinical Benefit Rate

CBRs were estimated by treatment arm based on the tumor response evaluation performed by the PI or designee according to RECIST 1.1 for CBR (CR, or PR, or dSD). The statistical significance of the difference in CBR between treatment arms were evaluated using the Cochran-Mantel-Haenszel (CMH) chi-square test with histology, geographic region and number of prior regimens for advanced STS as strata, tested at an alpha level of 0.05. A 95% 2-sided CI of the difference in CBR was constructed as well as similar CIs for the rate within treatment arm.

The Fixed Sequence procedure was used to control the overall type I error rate of analyses for secondary endpoints at $\alpha = 0.05$. The order of testing for secondary endpoints followed the order that they are presented above. The PFS endpoint was tested at the 5% level and if significant, the PFR_{12wks} endpoint was tested at the 5% level. If the PFS endpoint was not significant, then the results of the inferential analysis of the PFR_{12wks} and CBR endpoints were presented for descriptive purposes only.

Analysis of Exploratory Endpoints:

Efficacy:

The statistical significance of the treatment differences for ORR (CR or PR), DCR (CR, or PR, or SD) and dSD rate were evaluated using the CMH chi-square test with histology, geographic region and number of prior regimens for advanced STS as strata, tested at an alpha level of 0.05, respectively. A 95% CI of the difference in rate was constructed, as well as similar CIs for the rate within treatment arm.

No multiplicity adjustments were used for the exploratory efficacy endpoints.

Other:

The statistical significance of the treatment differences for ORR (CR or PR), DCR (CR, or PR, or SD) and dSD rate were evaluated using the CMH chi-square test with histology, geographic region and number of prior regimens for advanced STS as strata, tested at an alpha level of 0.05 respectively. A 95% CI of the difference in rate was constructed as well as similar CIs for the rate within treatment arm.

QoL scales, obtained through the QLQ C30 and EQ-5D questionnaires were analyzed and compared between the two treatment arms. Full details of this analysis are provided in a separate QoL document.

Pharmacokinetic and/or Pharmacodynamic Analyses

Pharmacokinetics:

Plasma concentration versus time data were analyzed using a population PK approach to estimate population PK parameters using subjects in the PK Analysis Set.

Pharmacodynamic:

The effect on soluble tissue, genetic and/or other biomarkers was summarized by treatment arm and overall for the PD Analysis Set.

Pharmacokinetic-Pharmacodynamic:

Exploratory/graphical analysis was conducted for PK/PD evaluations, and was followed a model based analyses.

PK, PD, and PK/PD analyses were finalized in a separate document prior to database lock.

Safety Analyses

All safety analyses were performed on the Safety Analysis Set. Safety data was summarized separately by treatment arm using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum, Q1, Q3 for continuous variables; n [%] for categorical variables). Safety variables included treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs and physical examination findings, 12-lead ECG results. Study Day 1 for all safety analyses refers to the date of randomization. Clinical laboratory parameters were also presented by baseline and number of cycle.

Sample Size Rationale

The primary basis for the sample size determination was estimated and based upon the required number of target events to detect a treatment difference in the comparison of the OS.

The estimated median OS of Arm B (dacarbazine) is approximately 6 months and an improvement of 2.5 months is considered to be of clinical importance, which translated to a median OS in Arm A (eribulin) of 8.5 months and a hazard ratio of 0.706. The overall false positive rate was set at 0.05 assuming a two-sided test and power at 90%.

Based upon these assumptions, the event target was estimated to be 353 events (deaths). Assuming an enrollment rate of 20 subjects per month, it was estimated that approximately 450 subjects were needed to be randomized to observe this number of events which, for a randomization ratio of 1:1, was a minimum of 225 per treatment arm.

It was estimated that this would take approximately 29.2 months (22.5 months enrolment and 6.7 months follow-up). The number of deaths was monitored on an ongoing basis, and the primary analysis was performed when the target number of ~353 events was observed across both treatment arms.

Interim Analyses

Periodic safety monitoring was conducted by the Data Monitoring Committee (DMC). An efficacy interim analysis was conducted when 70% of the target number (247) of events was observed. The interim analysis was performed by an independent statistical reporting team. Full details of the interim analysis are provided in

the SAP and DMC Charter.

Full details of the statistical methodology for the study are provided in the SAP.

Results

Subject Disposition/Analysis Sets

Efficacy

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics

Safety

- Overall, the incidence of TEAEs was similar in the eribulin and dacarbazine arms. The most frequently reported TEAE was neutropenia for subjects in the eribulin arm and thrombocytopenia in the dacarbazine arm.
  - Neutropenia was the most commonly reported TEAE of interest in the eribulin arm, with an overall incidence of 43.8% and Grade 3 or 4 incidence of 35.4% (the majority [33.6% of which were considered related to treatment). There were 2 treatment-related episodes of Grade 3 febrile neutropenia, and 1 subject discontinued study treatment due to neutropenic sepsis. The percentage of subjects who required dose reduction or dose interruption due to neutropenia was 13.7% and 11.5%, respectively. The overall incidence of peripheral neuropathy was 22.1% and 3.1% experienced Grade 3 neuropathy. The percentages of subjects who discontinued treatment, required a dose reduction or interruption due to peripheral neuropathy were 0.9%, 3.1%, and 1.8%, respectively.
- The most common AEs reported for subjects in the eribulin and dacarbazine treatment arms are consistent with the known safety profile for each drug.
- The number of deaths during the study or within 30 days of last dose of study drug was higher in the eribulin arm (6.6%) compared with the dacarbazine arm (4.0%) and the primary reason for death during the study in both arms was due to disease progression. A total of 2 deaths were reported as related to treatment during the study, and these were both in the eribulin arm. One additional death (due to septic shock) was reported as unrelated to eribulin treatment by the investigator but was considered to be possibly related to study drug by the sponsor.
- The incidence of SAEs was similar in both treatment arms.
- The most frequently reported SAEs were neutropenia in the eribulin arm and thrombocytopenia in the dacarbazine arm, and all were considered related to treatment.
- A total of 17 subjects (7.5%) in the eribulin arm and 11 subjects (4.9%) in the dacarbazine arm discontinued study drug due to 1 or more TEAEs.
- The most common TEAEs that led to treatment discontinuation were thrombocytopenia and fatigue in the eribulin arm (2 subjects [0.9%]) each), and thrombocytopenia in the dacarbazine arm (3 subjects [1.3%]).

Conclusions

This study, intended as a direct comparison to an active agent, provides substantial evidence for the efficacy of eribulin vs. dacarbazine in advanced STS as demonstrated by the statistically significant and clinically meaningful improvement in OS. This was supported by a small numerical benefit in PFS also favoring those subjects receiving eribulin over those receiving dacarbazine. For other measures of efficacy examined in this study the two medications appeared to be comparable.

The safety profile of eribulin has been shown to be acceptable and manageable in STS, consistent with the known safety profile of eribulin in advanced/metastatic breast cancer. Key safety measures such as deaths on treatment (or within 30 days of last treatment), SAEs, and discontinuations due to AEs are comparable between the 2 treatment arms. Overall, this study indicates a positive benefit-risk ratio for the use of eribulin in advanced STS.

Date of Report: 22 June 2015