2 STUDY SYNOPSIS

Name of Company: Eisai Inc	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Not applicable	Referring to Module 5 of the Dossier	
Name of Active Ingredient: Eribulin mesylate	Volume: Page:	

Study Title A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Eribulin Mesylate Administered Biweekly (Q2W) for Subjects With Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Metastatic Breast Cancer
Investigators/Sites Multicenter: 12 sites in United States (refer to Appendix 16.1.4 for the list of investigators and sites)
Publication (Reference) John Smith, et al. Phase 2 study evaluating the efficacy and safety of eribulin mesylate administered biweekly for patients with human epidermal growth factor receptor 2-negative metastatic breast cancer. The San Antonio Breast Cancer Symposium (SABCS), 2017, San Antonio.
Study Period 16 Jun 2015 to 31 Dec 2016 (primary database cutoff)
Phase of Development Phase 2
Objective(s) **Primary Objectives** • To evaluate efficacy of eribulin mesylate administered biweekly in terms of objective response rate (ORR) and disease control rate (DCR) in subjects with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC) previously treated with 2 to 5 chemotherapy regimens. **Secondary Objectives** • To evaluate the dose intensity of eribulin mesylate administered biweekly as measured by feasibility rates • To evaluate the efficacy of eribulin mesylate administered biweekly in terms of progression-free survival (PFS) and overall survival (OS). • To evaluate the safety and tolerability of eribulin mesylate administered biweekly **Exploratory Objectives** • To explore the efficacy of eribulin mesylate administered biweekly in terms of the clinical benefit rate • To explore the safety and tolerability of eribulin mesylate administered biweekly in terms of the relative dose intensity
Methodology This was a Phase 2, open-label, single-arm, multicenter, 2-stage study of eribulin mesylate administered biweekly at 1.4 mg/m^2 intravenously for the treatment of subjects with HER2-negative MBC previously treated with 2 to 5 chemotherapy regimens. The study consisted of 3 Phases: the Pretreatment Phase (Screening Visit),

the Treatment Phase (Starting Cycle 1 Day 1), and the Posttreatment Phase (End-of-Treatment Visit and survival Follow Up). The Pretreatment Phase (Day -21 to -1) included assessments before the first dose of study drug to establish eligibility and baseline values. The Treatment Phase started with the first dose of study drug and continued through the Cycle 1, 2, 3 and last cycle assessments. The Posttreatment Phase included an End of Treatment visit within 28 days of the last dose of study drug and a Follow-up Period (every 12-week assessments). Subjects were to remain on study treatment as long as they demonstrated clinical benefit or until intercurrent illness, unacceptable toxicity, or disease progression (PD) occurred, or until the subject withdrew consent. Subjects who discontinued treatment without evidence of PD had tumor assessments every 12 weeks in the posttreatment Follow-up Period until PD was documented or the subjects started another anticancer therapy or death, whichever occurred first. The study was conducted in 2 stages. Stage 1 assessed for futility in 17 evaluable subjects. An interim analysis using a modified Simon 2-Stage Design was conducted and the study was to be stopped early in the event of lack of efficacy, characterized by <1 responder (determined by ORR) and <8 responders (determined by DCR). The interim analysis boundary for continuing the study was crossed in at least 1 endpoint and therefore the study proceeded into Stage 2. Subjects in this study report include those enrolled in Stage 1 and Stage 2.

Number of Subjects (Planned and Enrolled)

Planned (Stage 1 and 2): 58 subjects (55 evaluable); Enrolled: 58 subjects; Assigned to treatment: 58 subjects.

Diagnosis and Main Criteria for Inclusion

Females aged ≥18 years were eligible to take part in the study if they had histologically confirmed HER2-negative MBC previously treated with 2 to 5 chemotherapy regimens. HER2 status was determined by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). Subjects were required to have measurable disease, defined as the presence of at least 1 measurable lesion, to be eligible for entry into the study. Measurable lesions were categorized at baseline as ≥10 mm in the longest diameter for a non-lymph node or ≥15 mm in the short-axis diameter for a lymph node as determined by the investigator using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1; Protocol, Appendix 2). Subjects had to have adequate renal, bone marrow and hepatic function. Subjects should not have had previous treatment with chemotherapy, radiation, biological or targeted within 2 weeks or 5x half-life prior to dosing (Cycle 1, day 1). Subjects with known central nervous system disease were excluded.

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

Eribulin mesylate: 1.4 mg/m^2 intravenous (IV) infusion (over 2 to 5 minutes) on Days 1 and 15 of each 28-day cycle. Eribulin mesylate was supplied in 1.0 mg per 2.0 mL of solution in 5-mL single-use vials. The following batch number was used in the study: N1200923 (expiry 25 Oct 2017).

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

Not applicable

Duration of Treatment

Subjects received eribulin mesylate for as long as they demonstrated clinical benefit or until intercurrent illness, unacceptable toxicity, or disease progression occurred, or until the subject withdrew consent.

Assessments

Efficacy: Tumor assessments using RECIST 1.1 were performed during the Pretreatment Phase, then every 8 weeks during the Treatment Phase and every 12 weeks during the Posttreatment Follow-up Period for subjects who did not have disease progression. Disease progression and response evaluation were determined by the investigator for each subject according to definitions established in the RECIST Guidelines (version 1.1; Protocol, Appendix 2). The same imaging methodology was used throughout the study.

Pharmacogenomics: Not applicable

Safety: Safety was assessed by the monitoring and recording of all treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and concomitant medications, routine laboratory parameters, vital sign measurements, electrocardiograms (ECGs), and physical examinations. Treatment-emergent adverse events (AEs) were defined as those AEs that occurred (or worsened, if present at Baseline) after the first dose of study drug through 30 days after the last dose of study drug.

Statistical Methods

Sample size: A total of approximately 58 subjects were planned to be enrolled in order to have 55 evaluable subjects (Evaluable Analysis Set). The final thresholds (boundaries) for success were defined in terms of ORR by at least 7 responders or in terms of DCR by at least 32 responders out of 55 evaluable subjects. Assuming an ORR of 15% in eribulin-treated subjects from this study vs. 5% and a DCR of 60% in the eribulin-treated subjects from this study vs. 45%, there was a 0.0488 probability of erroneously concluding that eribulin treatment administered biweekly is efficacious under the null hypothesis (Type I error) and a 0.1001 probability of rejecting an efficacious biweekly eribulin administration schedule under the alternative hypothesis (Type II error).

Co-Primary Endpoints: ORR, defined as the proportion of subjects who had best overall response (BOR) of Complete Response (CR) or Partial Response (PR). Confirmation of CR and PR must have been performed ≥4 weeks after response was first documented; DCR, defined as the proportion of subjects who had BOR of CR, PR, or Stable Disease (SD). Stable disease must be achieved at ≥7 weeks after the first eribulin administration to be considered BOR.

Secondary Endpoints: PFS, defined as the time from date of first dose of study drug to date of first documentation of PD or death, whichever occurred first; OS, defined as the time from the date of first dose of study drug until date of death from any cause; Feasibility Rate, defined as the percentages of subjects completing the first 2 and 4 cycles of eribulin treatment (4 and 8 doses) without requiring dose delay >5 days or reduction due to AE; Incidence of adverse events throughout study as reported by the Investigator. These events are graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 and coded according to Medical Dictionary for Regulatory Activities (MedDRA).

Exploratory Endpoints: Relative Dose Intensity, defined as the actual total dose of eribulin divided by the total planned dose of eribulin; Clinical Benefit Rate, defined as the proportion of subjects who had BOR of CR, PR, or durable SD (≥23 weeks).

Analysis Sets: Full Analysis Set [FAS] included all subjects who received any amount of study drug. This was the analysis set for efficacy and safety analyses. Evaluable Analysis Set [EAS] (subset of Full Analysis Set) included all subjects who have both an evaluable baseline tumor assessment and an evaluable post-baseline tumor assessment, unless the subjects discontinued because of PD or toxicity.

Interim analysis: An interim futility analysis was performed after 17 evaluable subjects in Stage 1 were enrolled and became eligible for the interim analysis. Based on preliminary efficacy results (ORR: 1 subject (5.9%); DCR: 11 subjects (64.7%), the null hypothesis was rejected in Stage 1 according to the decision rules presented in the table below and the study proceeded into Stage 2 as planned.

Efficacy analyses: The treatment effect of no clinical interest was ORR ≤5% and DCR ≤45%; and the treatment effect that was considered clinically meaningful was ORR >15% and DCR >60%. Hence, the two hypotheses of interest were:

- H0: ORR ≤5% vs. H1: ORR >15%;
- H0: DCR ≤45% vs. H1: DCR >60%

A modified Simon Two-Stage Design was used in hypothesis testing for the 2 primary endpoints. The interim futility analysis after Stage 1 allowed for an early evaluation of efficacy results in order to stop the study early in the case of low anticancer activity. The numbers of subjects in Stage 1 (approximately 15) and Stage 2 (approximately 40) were based on practical considerations. This design differed from combining two independent Simon Two-Stage designs in that a different interim decision rule was used. Instead of evaluating each endpoint independently and accepting H0 when it failed to pass the interim boundary, hypothesis tests in both endpoints were carried out at final analysis as long as the interim analysis boundary was crossed in at least one endpoint. This testing strategy was more intuitive and flexible than making separate interim decisions in each endpoint, avoiding the dilemma of accepting H0 when the final boundary was passed but the interim boundary was not passed. The sample size and thresholds (boundaries) at the end of each stage with decision rules specified for the design are shown in Table below. The characteristics of the design were calculated by exact binomial distribution and are confirmed via simulation. The probabilities of stopping the study early under the null and alternative hypotheses are estimated as 0.3028 and 0.0186, respectively. Type I and II errors in testing the hypothesis of ORR are estimated as 0.0183 and 0.2701, respectively. Type I and II errors in testing the hypothesis of DCR are estimated as 0.0311 and 0.3440, respectively. Overall Type I and II errors are

estimated as 0.0488 and 0.1001, respectively.

Stage	Endpoint	Boundary	Interim Analysis[a]	Final Analysis[b]
1 (n=15)	ORR	≥1	Continue if either boundary is crossed; otherwise, stop study and accept both H_0	
	DCR	≥8		
1+2 (n=55)	ORR	≥7		Reject H_0 if threshold is crossed[c]
	DCR	≥32		Reject H_0 if threshold is crossed[d]

DCR=Disease Control Rate; ORR = Objective Response Rate.
a: Performed after 15 evaluable subjects completed 3 cycles of treatment unless discontinued due to disease progression or toxicity.
b: Performed after all ongoing subjects completed at least 5 cycles of treatment or discontinued from treatment and at least 75% of subjects had disease progression or death event.
c: H_0: ORR ≤5%
d: H_0: DCR ≤45%

If the null hypothesis was rejected in Stage 1 according to the decision rules presented in the table above, the study proceeded into Stage 2 where 2 hypotheses were tested independently in the final analysis. The final analysis was done after all ongoing subjects completed at least 5 cycles of treatment or discontinued from treatment and at least 75% of subjects had disease progression or death event.

The biweekly eribulin dosing schedule was deemed efficacious if at least 1 of the 2 null hypotheses was rejected. A 2-sided Clopper-Pearson 95% confidence interval (CI) was also constructed for ORR and DCR in EAS.

Feasibility rates of completing the first 2 cycles and 4 cycles and their 95% Clopper-Pearson CIs were calculated in the FAS.

Progression-Free Survival and OS were analyzed using Kaplan-Meier product-limit estimates. Progression-Free Survival and OS rates at [3, 6, and 12] and [6, 12, 18] months respectively were presented with two-sided 95% CIs. The cumulative PFS and OS were plotted over time. The median, first, and third quartiles from Kaplan-Meier estimation for PFS and OS were provided with 95% Brookmeyer-Crowley CIs if estimable.

For Clinical Benefit Rate, a 2-sided Clopper-Pearson 95% CI was constructed for calculating exact binomial intervals. Rate estimates were compared with those from previous eribulin studies with a comparable patient population.

Safety Analyses: Safety analyses were performed by treatment group based on the FAS. Safety data was summarized on an "as treated" basis. The incidence of TEAEs and SAEs were summarized. Laboratory test results, vital signs and their changes from baseline were summarized using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables. Abnormal values were flagged.

Average dose intensity per subject (in mg/m^2/week and mg/m^2/day) and relative dose intensity (total dose received / total dose planned) per subject were summarized.

Results

Subject Disposition/Analysis Sets

A total of 58 subjects were enrolled and treated with eribulin mesylate.

All 58 subjects were included in the FAS and 57 subjects were included in the EAS.

Efficacy

Primary efficacy results for the EAS are provided in the following table.

Response Category	Eribulin N=57

Best Overall Response	
Complete response (CR), n (%)	1 (1.8)
Partial response (PR), n (%)	6 (10.5)
Stable Disease (SD), n (%)	30 (52.6)
Progressive Disease (PD), n (%)	19 (33.3)
Not Evaluable/Unknown; n (%)	1 (1.8)
Objective Response Rate (CR +PR); n (%)	7 (12.3)
95% CI	(5.08, 23.68)
Disease Control Rate (CR+PR+SD); n (%)	37 (64.9)
95% CI	(51.13, 77.09)

Subject PPD who withdrew from the study and had no post-baseline tumor assessment was excluded from the EAS.

Secondary efficacy results for the FAS are provided in the following table.

	Eribulin N=58
Progression-Free Survival (PFS), Months	
Median (95% CI)	3.6 (2.86, 4.07)
Kaplan Meier Estimate of PFS	
3-month PFS rate (95% CI)	0.62 (0.47, 0.73)
6-month PFS rate (95% CI)	0.23 (0.12, 0.36)
12-month PFS rate (95% CI)	0.10 (0.02, 0.23)
Overall Survival (OS), Months	
Median (95% CI)	13.2 (10.61, NE)
Kaplan Meier Estimate of OS	
6-month OS rate (95% CI)	0.84 (0.71, 0.91)
12-month OS rate (95% CI)	0.54 (0.38, 0.68)
18–month OS rate (95% CI)	NE (NE, NE)
Feasibility Rate[a], n (%) [95% CI]	
First 2 cycles	37 (69.8) [55.7, 81.7]
First 4 cycles	11 (50) [28.2, 71.8]

NE = Not evaluable

a: Feasibility rate is based on the total number of subjects completing the first 2 cycles (4 doses) and 4 cycles (8 doses) of eribulin treatment

Exploratory efficacy results for the FAS are provided in the following table.

Clinical Benefit Rate (CR+PR+durable SD); n (%)	17 (29.3)

95% CI	(18.09, 42.73)

Safety

An overview of the AE profile is summarized for the FAS in the following table.

Category	**Eribulin (N=58) n (%)**
TEAEs	58 (100.0)
Treatment-Related TEAEs	54 (93.1)
TEAEs with CTCAE Grade 3 and Above	43 (74.1)
Severe TEAEs (Grade 3 and 4)	43 (74.1)
Serious AEs	13 (22.4)
Deaths[a]	2 (3.4)
Other SAEs	
Requires inpatient hospitalization or prolongation of existing hospitalization	11 (19.0)
Important medical events	2 (3.4)
Life-threatening	1 (1.7)
Persistent or significant disability or incapacity	1 (1.7)
TEAEs leading to study drug dose adjustment	37 (63.8)
TEAEs leading to study drug interruption	32 (55.2)
TEAEs leading to study drug dose reduction	14 (24.1)
TEAEs leading to study drug withdrawal	1 (1.7)
Other events of special interest	
Neutropenia[b]	40 (69.0)
Peripheral Neuropathy[c]	27 (46.6)
Alopecia	26 (44.8)

a: One subject had a TEAE within 30 days of last dose of study drug but died >30 days after last dose of study drug.

b: Customized MedDRA Queries of neutropenia. The following terms are included: neutropenia and neutrophil count decreased.

c: Customized MedDRA Queries of peripheral neuropathy. The following terms are included: gait disturbance, muscular weakness, dysaesthesia, dysgeusia, hypoaesthesia, neuralgia, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy.

The most frequently reported TEAEs (≥20% of subjects), along with the corresponding incidences of severe events and treatment-related events are provided for the Safety Set in the following table.

	Eribulin (n=58)		
MedDRA Preferred Term	**All Grades n (%)**	**Grade ≥3 n (%)**	**Drug Related n (%)**

No. (%) of subjects with any TEAE	58 (100.0)	42 (74.1)	54 (93.1)
Fatigue	28 (48.3)	1 (1.7)	24 (41.4)
Alopecia	26 (44.8)	0	22 (37.9)
Neutropenia	23 (39.7)	18 (31.0)	21 (36.2)
Constipation	21 (36.2)	1 (1.7)	11 (19.0)
Neutrophil count decreased	20 (34.5)	16 (27.6)	20 (34.5)
Peripheral sensory neuropathy	16 (27.6)	5 (8.6)	14 (24.1)
Nausea	15 (25.9)	0	12 (20.7)
Diarrhea	12 (20.7)	1 (1.7)	3 (5.2)
Stomatitis	12 (20.7)	4 (6.9)	12 (20.7)

A total of 13 subjects reported an SAE and most events occurred in single subjects; events reported in more than 1 subject were sepsis (2 subjects 3.4%) and cancer pain (2 subjects 3.4%). One subject discontinued study drug due to an AE of platelet count decreased.

Two subjects (3.4%) died due to a non-treatment related TEAE. One subject died due to sepsis on Day 69, 27 days after the last dose of study drug and the event was considered by the investigator to be unrelated to study drug; the subject had been withdrawn from the study drug due to disease progression on Day 49. The second subject, experienced acute respiratory failure on Study Day 63 and died due to the event on Study Day 71, 34 days after the last dose; the event was considered by the investigator to be unrelated to study drug and was attributed to disease progression.

There were no clinically relevant trends in group mean/median lab or vital sign values over time.

Conclusions

In this small single arm hypothesis generating study the interim analysis boundary for continuing the study at Stage 1 was achieved. The study met its primary endpoints at the end of stage 2 final analysis, each null hypothesis for the co-primary endpoints (ORR and DCR) was rejected, therefore the biweekly eribulin dosing schedule was considered efficacious.

Tumor response rates and overall survival rates in heavily pretreated MBC subjects receiving the biweekly dosing regimen (Day 1 and Day 15, of 28 day cycle) were similar to previously reported studies with eribulin. The toxicities associated with biweekly eribulin were known and manageable, as previously reported in other trials with eribulin. Overall, this Phase 2 trial trial with a biweekly dosing schedule demonstrated similar efficacy and safety as reported in the larger clinical trials with eribulin using the approved dosing (1.4 mg/m^2 of eribulin mesylate on Days 1 and 8 of each 21-day cycle), however a trend of numerically higher neutropenia, than in previous trials, was observed. A larger trial is warranted to further explore the eribulin biweekly dosing.

Date of Report

09 Apr 2018