2. SYNOPSIS

Name of Sponsor/Company: Eisai Co., Ltd.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Name of Finished Product: Not yet determined		
Name of Active Ingredient: Eribulin mesylate (JAN)		
Title of study: Phase II Clinical Study of E7389 for Locally Advanced or Metastatic Breast Cancer		
Principal investigators: Kazunori Taguchi and others, 22 investigators in total (refer to Appendix 16.1.4a)		
Study centers: National Hospital Organization, Hokkaido Cancer Center and others, 22 centers in total (refer to Appendix 16.1.4.a)		
Publication (Reference of report on the results of this study) None		
Study period: One year and 8 months Jan 21, 2008 (date of consent by the first subject) Sep 11, 2009 (date of completion of the final test and observation in the last subject)	**Phase of development:** Phase II	
Objectives: **Primary**: To investigate the efficacy (objective response rate) and safety of intravenous administration of E7389 in patients with locally advanced or metastatic breast cancer **Secondary**: To evaluate the duration of overall response		
Methodology: Multi-center, non-randomized, open-label study		
Number of subjects (planned and analyzed): Planned: 78 – 82 subjects (at the time when 26 – 28 subjects become evaluable for tumor response, interim assessment will be performed.) Analyzed: Enrolled subjects 84, 80 subjects in full analysis set (FAS), 79 subjects in per protocol set (PPS) and 81 subjects in safety analysis set.		
Diagnosis and criteria for inclusion: Target disease: Advanced or relapsed breast cancer Inclusion criteria: Subjects who met all of the following criteria were included in the study. (1) Female patients with histologically or cytologically confirmed breast cancer (2) The following patients who have received prior chemotherapy with anthracycline and taxane: • Patients who had a relapse of breast cancer during or within 1 year after neoadjuvant or postoperative adjuvant therapy as chemotherapy immediately before this study. • Patients who had PD of breast cancer during or within 6 months after chemotherapy for progression or relapse of breast cancer immediately before this study. Previous chemotherapy for progression or recurrence of tumor is limited to 3 regimens or less. Hormone therapy, antibody therapy, immunotherapy or local radiotherapy does is not included in the number of regimens of previous therapy. (3) Patients aged between ≥20 and <75 years when giving informed consent (4) Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 (5) Patients with a measurable lesion* *: Tumor lesions which are accurately measurable in at least one dimension by CT or MRI and have maximum diameter longer than two times or more of slice width, more specifically, lesions of which size is 20 mm or more by conventional measuring method or 10 mm or more by helical CT and superficial lesions (such as skin metastasis) which are measurable by color photography with		

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caliper. Bone lesions are identified as non-targeted lesions.

(6) Patients having adequate function of major organs (bone marrow, liver, kidney and lung):
1) Neutrophil count ≥1,500/μL
2) Platelet count ≥100,000/μL
3) Hemoglobin ≥9.0 g/dL
4) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times the upper limit of normal (ULN) established in the study centers.
However, ≤ 5.0 times of ULN in patients with hepatic metastasis
5) Total bilirubin ≤ 1.5 times of ULN established in the study centers
6) Serum creatinine ≤ 1.5 times of ULN established in the study centers

(7) Patients who currently do not have effect of the previous therapy or adverse drug reactions occurred in the previous therapy which may affect safety evaluation of the study drug (excluding alopecia and neuropathy of Grade 1).
For subjects who received any previous therapy specified below, the following washout period should be included between completion of the previous therapy and the start of study drug administration. And the washout period of other study drugs is decided according to the below category 1) to 3).
1) Antibody preparations for treatment of malignant tumor, chemotherapy (excluding oral 5-FU and molecular targeting drugs), surgical therapy: ≥ 4 weeks
2) Nitrosoureas and mitomycin C: ≥ 6 weeks
3) Radiotherapy, endocrine therapy, immunotherapy (excluding pleurodesis with picibanil), oral 5-FU, molecular targeting drugs*, blood transfusion, blood preparations, hematopoietic factor preparations such as G-CSF: ≥ 2 weeks

* For antibody preparations such as trastuzumab, washout period should be 4 weeks or more).

(8) Patients who have given written informed consent for participation in this study

(9) Patients with an expected survival of ≥ 3 months from the start of study drug therapy

Exclusion criteria:

Subjects who fell under any of the following criteria were excluded from the study.

(1) Patients with systemic infection with a fever (≥38.0°C)

(2) Patients with pleural effusion, ascites or pericardial fluid requiring drainage

(3) Patients with brain metastasis presenting clinical symptoms

(4) Patients with serious complications shown below:
1) Patients with ischemic heart disease not controllable by treatment or heart disease such as arrhythmia (excluding left ventricular hypertrophy and mild left ventricular volume overload associated with hypertension, and mild right-bundle block)
2) Patients who had myocardial infarction within 6 months prior to study entry
3) Patients with a complication of hepatic cirrhosis
4) Patients with interstitial pneumonia or pulmonary fibrosis
5) Patients with a bleeding tendency

(5) Patients with an active double cancer

(6) Women who are pregnant or breast-feeding; premenopausal women of child-bearing potential. Premenopausal women who have child-bearing potential are defined as those who had the final menstruation within last 12 months, who had positive reaction in pregnancy test performed at the time of registration or received no pregnancy test, or who do not agree to use of appropriate contraception. To confirm no child-bearing potential, even premenopausal women have to have amenorrheic period for

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at least 12 months.
(7) Patients who require continuous steroid systematic treatment during the study period
(8) Patients who require continuous use of drugs that inhibit the drug metabolizing enzyme CYP3A4 or drugs or foods that induce CYP3A4 during the study period
(9) Patients who have received extensive radiotherapy (≥30% of bone marrow)
(10) Patients who refuse to receive the supportive therapy of blood transfusion for myelosuppression, etc.
(11) Patients who are participating in other clinical studies
(12) Patients who are judged inappropriate for this study by the investigator or subinvestigator

Test product, reference product, dose and mode of administration, lot number

Test product: E7389
Reference product: None
Dose and mode of administration:

Defining the day of the initial administration of E7389 as Day 1, 1.4 mg/m^2 of E7389 was intravenously administered over 2 – 5 minutes on Day 1 and Day 8, and administration was interrupted up to Day 21. If an adverse drug reaction which falls under any one of the dose-reduction criteria is noted in a cycle, the dose in the next cycle was to be reduced to one level lower than the dose in the previous cycle. Dose-reduction was made in the order of 1.4 mg/m^2 → 1.2 mg/m^2 → 1.0 mg/m^2 → 0.7 mg/m^2.

[Criteria for dose reduction]
(1) ≥Grade 3 febrile neutropenia
(2) ≥Grade 3 neutropenia (<1,000/μL) with infection which requires antibiotic treatment (iv)
(3) Grade 4 thrombocytopenia (<25,000/μL)
(4) ≥Grade 3 non-hematologic toxicity (excluding nausea, vomiting, anorexia and laboratory abnormalities with no clinical symptoms)
(5) Omission of the administration on Day 8 within the cycle due to any of the following adverse drug reactions or cases:
  1) ≥Grade 3 neutropenia (<1,000/μL)
  2) ≥Grade 3 thrombocytopenia (<50,000/μL)
  3) Cases where the investigator or subinvestigator has judged it appropriate to skip the administration.

Lot number: P5Y008ZZA for E7389 2 mL vial

Duration of treatment:

Defining one cycle as 3 weeks (21 days), the study drug was administered for 2 cycles or more in principle. After the initial administration of E7389 in a subject, administration was continued up to the time when the subject falls under any one of the criteria for study discontinuation. If a subject was confirmed to have best overall response and does not fall under any of the criteria for study discontinuation, the subject was to be eligible for continuing to receive E7389 therapy under another protocol.

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Criteria for evaluation:

Primary endpoint:

Tumor response (objective response rate) and safety (adverse event, adverse drug reaction etc.)

Secondary endpoint: Duration of overall response in subjects with objective response

Subjects' baseline characteristics: First diagnosis, presence or absence of relapse, status of expression of HER2/neu, sensitivity to hormones (ER, PgR), medical history, prior treatment history, primary lesion, metastatic lesion, complication, gender, age, height, body weight, body surface area

Efficacy:

Primary evaluation variable: Tumor response (objective response rate) (to be assessed according to RECIST)

Secondary evaluation variables: Duration of overall response in subjects with objective response (a period from the time when a subject is confirmed to meet the criteria for CR or PR to the first day when recurrence or PD is objectively confirmed in the subject), progression-free survival (a period from the time when a subject is registered to the day when PD or death by any causes is confirmed in the subject, whichever is earlier), and overall survival (a period from the time when a subject is registered to the day when death by any causes of the subject is confirmed).

Safety:

Adverse events (evaluated according to CTCAEv3.0 Japanese version), adverse drug reactions, electrocardiogram (ECG), symptoms and signs, physical examination findings [blood pressure, heart rate, body temperature, performance status (PS)], chest X-ray, pregnancy test, body weight and values of the following laboratory tests.

- Hematology: White blood cell count, neutrophil count, lymphocyte count, erythrocyte count, hemoglobin content and platelet count
- Blood biochemistry: Total protein, total cholesterol, blood glucose, albumin, total bilirubin, BUN, Al-P, AST, ALT, γ-GTP, LDH, CPK, serum electrolytes (Cl, Na, K, Ca, P), serum creatinine and CRP
- Urinalysis: Protein, (qualitative), glucose (qualitative) and occult blood
- SpO_2

Statistical methods:

Statistical analyses were performed using statistical analysis software SAS for Windows (release 8.2 or higher) and Microsoft Excel.

(1) Analysis of baseline characteristics of subjects

In safety analysis set, FAS and PPS, summary statistics were calculated using number of subjects, mean, standard deviation, median, minimum and maximum. For continuous variables classified by category and categorical variables, frequency and percentages were calculated.

(2) Efficacy analysis

1) Analysis of objective response rate

Best overall responses (Independent review and Investigator's assessment) were analyzed in FAS and PPS by calculating the number and percentages of patients assigned to CR, PR, SD, PD or NE. The number and percentages (objective response rate) of objective response subjects (CR+PR), the number and percentages (disease control rate) of subjects assessed as CR, PR or SD and the number and percentages (clinical benefit rate) of subjects assessed as CR, PR or SD of at least 6 months, and their exact 90% and 95% confidence intervals based on binominal distribution were calculated.

2) Analysis of duration of overall response

Duration of overall response of objective response subjects (Independent review and Investigator's assessment) in FAS and PPS were tabulated by Kaplan-Meier method and medians and their 95% confidence intervals were calculated.

3) Bayesian analysis of objective response rate

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For objective response rates, predictive posterior probabilities that true objective response rates are lower than 10%, 15% and 20% were calculated from the posterior distribution *Be* (0.5+*X*, 0.5+*N*−*X*) for number of analyzed subjects *N* and number of objective response subjects *X* by Bayesian approach using Jeffreys non-informative prior distribution [Beta distribution *Be* (0.5, 0.5)] in FAS and PPS. In addition, the mode, 95% equal tail credible interval and 95% highest posterior density credible interval of the posterior distribution for objective response rate were calculated.

4) Progression-free survival

Summary statistics of progression-free survival (number of subjects, median, minimum and maximum) and 95% confidence interval of median were calculated by Kaplan-Meier method. Number and percentages of subjects with events and censored in analysis set were calculated. Progression-free survival rates at Month 3, 6, 9 and 12 and their 95% confidence intervals were calculated using Kaplan-Meier method. Kaplan-Meier plot of progression-free survival was prepared together with At Risk.

5) Overall survival

Summary statistics of overall survival (number of subjects, median, minimum and maximum) and 95% confidence interval of median were calculated by Kaplan-Meier method. Number and percentages of subjects with events and censored in analysis set were calculated. Overall survival at Month 6 and 12 and their 95% confidence intervals were calculated using Kaplan-Meier method. Kaplan-Meier plot of overall survival was prepared together with At Risk.

6) Tumor markers and percent changes and maximum percent changes and sum of the longest diameter of target lesions

For clinical benefit subjects, figures showing percent changes by subject in sum of the longest diameter of target lesions over the study period on the ordinate and assessment timing (days from Day 1 of the first cycle) on the abscissa were prepared. In addition, figures showing changes by subject in each tumor marker over the study period on ordinate and measurement timing on the abscissa were prepared.

Waterfall plots showing maximum percent changes in sum of the longest diameter of target lesions on the ordinate in the order of subjects with larger maximum percent changes were prepared.

(3) Safety analysis

1) Analysis of adverse events

Number of adverse events, number of subjects with adverse events and incidences of adverse events were compiled in safety analysis set. Incidences were calculated as percentages of subjects with at least one adverse event and subjects with adverse events by system organ class (SOC) and by preferred term (PT) of adverse events in safety analysis set. Adverse events were also compiled by causal relationship with the study drug and by severity (CTCAEv3.0 Japanese version). For adverse events which are considered to be significant, time to onset and time to recovery were also compiled.

2) Analyses of laboratory test values, physical examination findings and body weight

For continuous variables, summary statistics of number of data, mean, standard deviation, standard error, median, minimum and maximum were calculated, and for categorical variables, frequencies and percentages were calculated in the safety analysis set.

Number of subjects with significant Treatment Emergent Abnormal Laboratory Values (TEAV) and incidences of TEAV were calculated for each test item shown in CTCAEv3.0 Japanese version.

Summary – Conclusions

Efficacy results:

Of the 80 subjects in FAS, 17 subjects were assessed as objective response cases (PR in all subjects) by Assessment Committee (independent review) and objective response rate, one of the primary endpoints of

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this study, was 21.3% (95% confidence interval: 12.9 – 31.8%). In FAS, 47 subjects were assessed as disease control (CR+PR+SD) by the independent review and disease control rate was 58.8% (95% confidence interval: 47.2 – 69.6%) and 22 subjects were assessed as clinical benefit (CR + PR +SD of at least 6 months) and clinical benefit rate was 27.5% (95% confidence interval: 18.1 – 38.6%). For objective response rates by the independent review, the mode of the posterior distribution calculated using Jeffreys non-informative prior distribution [Beta distribution *Be* (0.5, 0.5)] by Bayesian approach was 20.9%, the predictive posterior probabilities that true objective response rates were lower than 10%, 15% and 20% were 0.1%, 6.4% and 38.0% respectively, and 95% equal tail credible interval and 95% highest posterior density credible interval of true objective response rates were 13.4 – 31.1% and 13.0 – 30.6% respectively.

The median (95% confidence interval) of duration of overall response by the independent review was 119.0 days (85.0 – 148.0 days).

The median (95% confidence interval) of progression-free survival by the independent review was 112 days (61.0 – 133.0 days), and progression-free survival rates at Month 3, 6, 9 and 12 were 54.2%, 20.1%, 10.1% and 6.7% respectively.

Though number of subjects with event (death) was 41 in 80 subjects (51.3%) being small, median (95% confidence interval) of overall survival was 331.0 days (234.0 days – uncalculable), and 6-month and 12-month survival rates were 72.3% and 45.4% respectively.

Since the analytical results of the primary and secondary endpoints showed no large differences between FAS and PPS, the selection of analysis sets appeared to have only slight influence on the conclusion concerning the efficacy of E7389 in this study.

Subgroup analyses, stratifying FAS by age, tissue types, number of prior chemotherapy regimens, with or without administration of capecitabine and vinorelbine in prior chemotherapy, number of prior chemotherapy regimens for locally advanced or metastatic breast cancer, presence or absence of relapse, presence or absence of primary lesion or metastatic lesion, presence or absence of drug refractory, HER2/neu expression status, and sensitivity to hormones (ER and PgR), were performed, so that no factor appeared to clearly influence the evaluation of efficacy in this study.

Safety results:

The incidence of adverse events in safety analysis set was 100% (81/81 subjects). Adverse events with high incidences were leukopenia (98.8%, 80/81 subjects), neutropenia (98.8%, 80/81 subjects), alopecia (58.0%, 47/81 subjects) and lymphopenia (54.3%, 44/81 subjects). Incidences of adverse events of which causal relationship with the study drug could not be denied (adverse drug reactions) was 100% (81/81 subjects). Adverse drug reactions with high incidences included leukopenia (98.8%, 80/81 subjects), neutropenia (98.8%, 80/81 subjects), alopecia (58.0%, 47/81 subjects) and lymphopenia (54.3%, 44/81 subjects).

Death during the treatment period or within 30 days after the final administration occurred in one subject. Cause of the death was acute aggravation of the primary disease. Serious adverse events other than death included 21 events in 13 subjects. The serious adverse events of which causal relationship with the study drug could not be denied were anorexia, stomatitis and infection (each 2 events in 2 subjects), gastritis haemorrhagic, neutropenia, pyrexia, interstitial pneumonia, nausea and oedema (each 1 event in 1 subject). The serious unexpected adverse drug reactions of which occurrence cannot be expected from the Investigator's Brochure were gastritis haemorrhagic and oedema (each one event in one subject).

Adverse event led to discontinuation of study drug administration and adverse event of Grade 3 or 4 were defined as significant adverse event in this study. Six (6) subjects discontinued study drug administration due to adverse events, each of which varied among the subjects and did not occur in 2 or more subjects. Incidence of adverse events of Grade 3 or 4 was 96.3% (78/81 subjects), of which events with high

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incidences were neutropenia (95.1%, 77/81subjects), leukopenia (74.1%, 60/81 subjects), febrile neutropenia (13.6%, 11/81 subjects), lymphopenia (12.3%, 10/81 subjects) and gamma-glutamyltransferase increased (12.3%, 10/81 subjects). Adverse drug reactions of Grade 3 or 4 with high incidences were neutropenia (95.1%, 77/81subjects), leukopenia (74.1%, 60/81 subjects), febrile neutropenia (13.6%, 11/81 subjects), lymphopenia (12.3%, 10/81) and gamma-glutamyltransferase (γ-GTP) increased (6.2%, 5/81 subjects). Adverse events of Grade 4 included neutropenia (70.4%, 57/81 subjects), leukopenia (11.1%, 9/81 subjects) and interstitial pneumonia (1.2%, 1/81 subjects), and these adverse events were considered to be adverse drug reactions.

For laboratory test values, if grade of a pre-administration value is 0 (normal value), 1 or 2 and grade of post-administration value is 3, 4 or 5, or if grade of a pre-administration value is 3 or 4 and grade of post-administration value is worsened from pre-administration value, the post-administration value was defined as significant Treatment Emergent Abnormal Laboratory Values (TEAV). Overall incidence of TEAV was 77.8% (63/81 subjects). Laboratory test items with high incidence of TEAV were neutrophil count (95.1%, 77/81 subjects), white blood cell count (74.1%, 60/81 subjects), γ-GTP (17.3%, 14/81 subjects) and lymphocyte count (13.6%, 11/81 subjects).

For white blood cell count, neutrophil count and lymphocyte count, change in grade from pre-administration to post-administration, time to occurrence of changes to Grade 3 or 4 and time to recovery from the changes of Grade 3 or 4 were examined. Grade of white blood cell count was worsened after administration in most subjects. Before administration, white blood cell count was Grade 0 in 91.4% (74/81) of subjects, while after administration, it was worsened from Grade 0 to Grade 3 in 58.0% (47/81) of subjects and from Grade 0 to Grade 4 in 8.6% (7/81) of subjects. Median (range) of time to occurrence of changes to Grade 3 or 4 was 15.0 days (6+ – 36+ days), and median (range) of time to recovery from the changes of Grade 3 or 4 to Grade 1 was 8.0 days (1+ – 22 days). Grade of neutrophil count was also worsened after administration in most subjects. Before administration, neutrophil count was Grade 0 in 97.5% (79/81) of subjects, while after administration, it was worsened from Grade 0 to Grade 4 in 67.9% (55/81) of subjects and from Grade 0 to Grade 3 in 24.7% (20/81) of subjects. Median (range) of time to occurrence of changes to Grade 3 or 4 was 15.0 days (6+ – 36+ days), and time to recovery from the changes of Grade 3 or 4 to Grade 1 was 8.0 days (1+ – 21 days). For lymphocyte count, some subjects had no worsening in grade, and lymphocyte count was Grade 0 before and after administration in 27.2% (22/81 subjects), the largest number of subjects. In 24.7% (20/81) of subjects, Grade 0 of lymphocyte count before administration was worsened to Grade 2 after administration, and Grade 0 before administration was worsened to Grade 3 in 3.7% (3/81) of subjects, worsened from Grade 1 to grade 3 in 2.5% (2/81) of subjects and worsened from Grade 2 to grade 3 in 7.4% (6/81) of subjects. No subject had worsening to Grade 4. Median of time to occurrence of changes to Grade 3 or 4 could not be calculated due to small number of subjects who had worsening, and minimum and maximum time were 5 days and 39+ days. Median (range) of time to recovery from the changes of Grade 3 or 4 to the grade at baseline was 8.0 days (3 – 15+ days). (The mark of " +" shows censored data)

Symptomatic therapy with G-CSF for neutropenia was performed in 25.9% (21/81) of subjects. For white blood cell count, neutrophil count and lymphocyte count, time to occurrence of changes to Grade 3 or 4 and time to recovery from the changes of Grade 3 or 4 were compiled by subjects with or without G-CSF therapy. There was no clear difference between subjects received and not received G-CSF therapy. There were also no clear difference in time to occurrence of changes in white blood cell count, neutrophil count and lymphocyte count to Grade 3 or 4, and time to recovery from the changes of Grade 3 or 4 among doses.

Conclusion:

In patients who have received prior chemotherapy with anthracycline and taxane and had a relapse of breast cancer during or within 1 year after neoadjuvant or postoperative adjuvant therapy immediately

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before this study, and patients who have received prior chemotherapy with anthracycline and taxane and had PD of breast cancer during or within 6 months after chemotherapy for progression or relapse of breast cancer immediately before this study, E7389 was intravenously administered at a dose of 1.4 mg/m^2 over 2 – 5 minutes on Day 1 and Day 8 according to 3-week-one-cycle administration schedule. The results indicated that E7389 has anti-tumor activity. The major adverse drug reactions were leukopenia, neutropenia and alopecia, but these adverse drug reactions were controllable by means of supportive therapy, dose reduction of E7389, interruption or postponement of drug administration.

From these findings, it may be concluded that E7389, when used with attention to the safety, is a beneficial drug for patients with locally advanced or metastatic breast cancer.

Date of the report: Mar 18, 2010