SYNOPSIS

Sponsor	Eisai Europe Ltd.	
Name of test drug	E7389 (Eribulin)	
ClinicalTrials.gov Identifier	NCT02225470	
Title of Study	An Open-label Randomized Parallel Two-arm Multicenter Study of Eribulin Versus Vinorelbine in Female Subjects with Locally Recurrent or Metastatic Breast Cancer, Previously Treated with At Least Two and a Maximum of Five Prior Chemotherapy Regimens, Including an Anthracycline and a Taxane	
Group Leader Unit Principal Investigator	Cancer Hospital Chinese Academy of Medical Sciences. Professor Bing-He Xu	
Study Centers	35 sites in China	
Study Period	Began on 26 Sep 2013	Data cut-off on 29 Jan 2016
Clinical Phase	Phase 3	
Study Objectives	**Primary Objectives** • Evaluate Progression-Free Survival (PFS) for two treatment groups • Characterize the pharmacokinetic (PK) profile of eribulin **Secondary Objectives** • Evaluate for both treatment arms the following： – Overall Survival（OS） – Objective Response Rates（ORR） – Duration of Response • Evaluate safety parameters such as electrocardiograms (ECGs), vital signs (VS), adverse events (AEs), and laboratory measurements **Exploratory Objectives were to evaluate for both treatment arms the following** • Clinical Benefit Rate（CBR：Proportion of subjects with complete response[CR]+partial response[PR]+duration of stable disease[SD] ≥24 weeks） • Disease Control Rate（DCR：Proportion of subjects with CR + PR + SD at ≥12 weeks） • Durable Stable Disease（dSD）Rate：Proportion of subjects with duration of stable disease(SD)≥24 weeks • Association between the efficacy of eribulin or vinorelbine and βIII-tubulin (TUBB3) expression in tumor tissues or single nucleotide polymorphisms (SNPs) fo TUBB3 and cytochrome P450 gene	

<table>
<tr><td></td><td>And for Arm A（eribulin）:
Explored the relationship between exposure to eribulin and adverse events
Characterize the relationship between exposure to eribulin and OS, PFS and tumor size</td></tr>
<tr><td>Study Design</td><td>This study was designed as an open-label, randomized, parallel two-arm multicenter efficacy, pharmacokinetics and safety study of intravenously administered eribulin versus intravenously administered vinorelbine. Eligible female subjects would have measurable disease according to RECIST 1.1. Subjects would be enrolled and randomized in a 1:1 ratio to one of two arms as follows: Arm A, eribulin on Days 1 and 8 in multiple 21-day (three-week) cycles, and Arm B, vinorelbine on Days 1, 8 and 15 in multiple 21-day (three-week) cycles.

Randomization would follow a predefined randomization scheme using the following stratification factors: receptor status (Her2/neu positive, Her2/neu negative [triple negative], Her2/neu negative [non-triple negative], or Her2/neu unknown); and prior chemotherapy numbers (2～3 or 4～5).

The randomization of subjects to study groups (Arm A, eribulin; Arm B, vinorelbine) would be performed centrally by an interactive web response system (IWRS) using a randomization scheme reviewed and approved by an independent statistician.

The primary analysis (PFS) would be conducted when the target number of events (380 progression events or deaths prior to disease progression based on independent radiologic review) among the two treatment groups had been observed.

The study included three phases: Pre-randomization, Randomization treatment, and Follow-up visit.</td></tr>
<tr><td>Number of Subjects</td><td><table>
<tr><th></th><th>Eribulin</th><th>Vinorelbine</th><th>Total</th></tr>
<tr><td>Enrolled (signed informed consent)</td><td>NA</td><td>NA</td><td>648</td></tr>
<tr><td>Randomized</td><td>264</td><td>266</td><td>530</td></tr>
<tr><td>Treated</td><td>264</td><td>259</td><td>523</td></tr>
<tr><td>Completed Treatment</td><td>194</td><td>166</td><td>360</td></tr>
<tr><td>Full Analysis Set</td><td>264</td><td>266</td><td>530</td></tr>
<tr><td>Per Protocol Analysis Set</td><td>256</td><td>239</td><td>495</td></tr>
<tr><td>Safety Analysis Set</td><td>264</td><td>257</td><td>521</td></tr>
<tr><td>PK Analysis Set</td><td>17</td><td>0</td><td>17</td></tr>
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Subjects Selection	**Inclusion Criteria:** 1. Female subjects with histologically or cytologically confirmed carcinoma of the breast. 2. Subjects with locally recurrent or metastatic disease who had received at least two, and a maximum of five, prior chemotherapeutic regimens for breast cancer, at least two of which were administered for treatment of locally recurrent or metastatic disease. Prior therapy must be documented by the following criteria prior to entry into the study： a. Regimens must have included an anthracycline (e.g., doxorubicin, epirubicin), and a taxane (e.g., paclitaxel, docetaxel) in any combination or order. Prior treatment with any of these agents was not required if the agents were contraindicated for a prospective subject and documented in her medical history. b. Some of these regimens might have been administered as adjuvant and/or neoadjuvant therapy, but at least two must have been given for locally recurrent or metastatic disease. c. Subjects must have proven refractory to the most recent chemotherapy as documented by progression on or within 6 months of their last chemotherapy. d. Subjects with Her2/neu positive tumors might also have been treated with any Her2/neu targeted agents including antibodies, small compounds or investigational drugs. e. Subjects might also have been treated with antihormonal therapy. 3. Measurable lesion met the following criteria： a. At least one lesion of ≥1.0 cm in the longest diameter for a non-lymph node, or ≥1.5 cm in the short-axis diameter for a lymph node which was serially measurable according to RECIST 1.1 using computerized tomography/magnetic resonance imaging (CT/MRI). If there was only one target lesion and it is was non-lymph node, it should have a longest diameter of ≥1.5 cm. b. Lesions that had had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease based upon RECIST 1.1 to be used as a target lesion. 4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2. 5. Life expectancy of ≥3 months

	6. 18 years old≤Age≤70 years old at the time of informed consent 7. Adequate renal function as evidenced by serum creatinine ≤2.0 mg/dL, or a calculated creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula. 8. Adequate bone marrow function as evidenced by absolute neutrophil count (ANC) ≥1.5 x 10^9/L, hemoglobin ≥10.0 g/dL, and platelet count ≥100 x 10^9/L. 9. Adequate liver function as evidenced by bilirubin ≤1.5 times the upper limits of normal (ULN); and alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3.0 times ULN (in the case of liver metastases ≤5.0 times ULN). 10. Subject willing and able to comply with the study protocol for the duration of the study. 11. All female subjects would be considered to be of child-bearing potential unless they were postmenopausal (at least 12 months consecutive amenorrhea, in the appropriate age group and without other known or suspected cause), or had been sterilized surgically (i.e., bilateral tubal ligation ≥1 menstrual cycle prior to randomization, or had undergone a hysterectomy and/or bilateral oophorectomy). Female subjects of child-bearing potential must agree to use two forms of highly effective contraception from the last menstrual period prior to randomization (or use a double barrier method as described below until they are on two forms of highly effective contraception for at least one menstrual cycle), during study treatment, and for 3 months after the final dose of study treatment. Female subjects exempt from this requirement were subjects who practiced total abstinence. If currently abstinent, the subject must agree to use a double barrier method of contraception, i.e. condom and occlusive cap (diaphragm or cervical/vault caps) with spermicide or until they are on two forms of highly effective contraception for at least one menstrual cycle if they became sexually active during study treatment and for 3 months after the final dose of study treatment. Highly effective contraception includes： a. Placement of intrauterine device or system, b. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault cap) with spermicide, c. Established hormonal contraceptive methods: oral, injectable or implant. Female subjects who were using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product from the last menstrual period prior to randomization, and must continue to use the same hormonal contraceptive product during study treatment,

	and for 3 months after the final dose of study treatment,； d. Vasectomized partner with confirmed azoospermia. 12. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol, with the understanding that the patient may withdraw consent at any time without prejudice.
	Exclusion Criteria: 1. Subjects who had received any of the following treatments within the specified period before treatment start: a. Vinorelbine had been administered as neoadjuvant or adjuvant therapy within one year. b. Chemotherapy, radiation, Her2/neu targeted agents including trastuzumab or hormonal therapy within three weeks. c. Any investigational drug within four weeks. d. Blood transfusion, blood preparations and hematopoietic factor preparations such as G-CSF within two weeks 2. Subjects of advanced breast cancer with vinorelbine effective therapy to CR/PR/SD, and PD occurred after vinorelbine discontinuing within 6 months. 3. Subjects with ineffective prior vinorelbine treatment. 4. Pulmonary lymphangitic involvement that resulted in pulmonary dysfunction requiring active treatment, including the use of oxygen. 5. Subjects with brain or subdural metastases were not eligible, unless they had completed local therapy and had discontinued the use of corticosteroids for this indication for at least four weeks before starting treatment in this study. Any signs (e.g., radiologic) and/or symptoms of brain metastases must be stable for at least four weeks before starting study treatment; and radiographic stability should be determined by comparing a contrast-enhanced CT or MRI brain scan performed during screening to a prior scan performed at least four weeks earlier. 6. Subjects with meningeal carcinomatosis. 7. Woman must not be pregnant as documented by a negative beta-human chorionic gonadotropin (ß-hCG) test with a minimum sensitivity 25 IU/L, or equivalent unit of ß-hCG, at Screening and Baseline; nor breastfeeding. 8. Severe/uncontrolled intercurrent illness/infection. 9. Significant cardiovascular impairment (history of congestive heart failure

	greater than New York Heart Association (NYHA) Class II, unstable angina or myocardial infarction within the past six months, or serious cardiac arrhythmia). 10. Subjects with organ allograft requiring immunosuppression therapy. 11. Subjects with known positive human immunodeficiency virus (HIV) status. 12. Subjects who had had a prior malignancy, other than breast cancer, carcinoma in situ of the cervix, or non-melanoma skin cancer, unless the prior malignancy was diagnosed and definitively treated at least five years previously with no subsequent evidence of recurrence. 13. Subjects with preexisting neuropathy >Grade 2. 14. Subjects with a hypersensitivity to halichondrin B and/or a halichondrin B chemical derivative. 15. Subjects who participated in a prior eribulin clinical trial whether or not eribulin was received. 16. Known intolerance to eribulin or vinorelbine (or any of the excipients). 17. Any medical condition that in the investigator's opinion might preclude subject from being entered in the study.
Strengths and batch number	• **Test Product**：Eribulin Mesylate Injection 2.0ml:1.0mg * 1 vial, Supplied by NerPhaMa Batch No. N1200067, EXP DATE: Dec 2015; Batch No.N1301144, EXP DATE: Sep 2017. • **Reference Product:** Vinorelbine Tartrate Injection，1ml:10mg*1 vial Supplied by Pierre Fabre Medicament Production-Aquitaine Pharma International Batch No.:2P129，EXP DATE: Oct 2015; Batch No.: 1P134, EXP DATE: Mar 2016; Batch No.2P137, EXP DATE: Sep 2016.
Dose and Mode of Administration	• **Test Group:**E7389（Eribulin） The eribulin mesylate dose would be 1.4 mg/m^2 administered as an intravenous bolus over 2 to 5 minutes on Days 1 and 8 of each 21-day cycle. • **Active Control Group:** Vinorelbine The vinorelbine dose would be 25 mg/m^2 administered as an intravenous bolus on Days 1, 8, and 15 of each 21-day treatment cycle.
Criteria for Evaluation:	**Efficacy Endpoint:** **Primary Efficacy Endpoint:**

- Progression-Free Survival（PFS）, defined as the time from the date of randomization to the date of first documentation of disease progression, or to the date of death from any cause, whichever occurs first. PFS censoring rules would be defined in the SAP and follow FDA guidance.

Secondary Efficacy Endpoint:

- Overall Survival（OS）, defined as the time from the date of randomization until the date of death from any cause.
- Objective Response Rate（ORR）,defined as the proportion of subjects who have best overall response of CR, or PR.
- Duration of Response, defined as the time from the date that an objective response (CR or PR) was first documented to the date of disease progression (PD) or the date of death due to any cause in the absence of PD with the subject who had CR or PR.

Exploratory Endpoints：

- Clinical Benefit Rate（CBR）, defined as the proportion of subjects with CR + PR + durable SD with a duration of SD ≥24 weeks.
- Disease Control Rate（DCR）, defined as the proportion of subjects with CR + PR + SD at ≥12 weeks.
- Durable Stable Disease（dSD）Rate, defined as the proportion of subjects with duration of SD ≥24 weeks.
- Time to treatment failure (TTF), defined as time from the date of randomization to the date of study treatment discontinuation due to any cause.

Pharmacokinetics:

For pharmacokinetic (PK) sampling, blood would be collected from subjects in the eribulin arm only (Arm A) during the Randomization Phase at selected investigator sites. Samples would be collected from a minimum of 15 subjects during Cycle 1 on Day 1 and Day 8 at predose, end of infusion and at 15 min., 30 min. and 1, 2, 4, 6, 10, 24, 48, 72, 96, 120, 144, and 168 hours after start of infusion

Others:

βIII-tubulin (TUBB3) expression in tumor tissues

The expression of TUBB3 in tumor tissues would be measured by immunohistochemistry (IHC) method.

Single nucleotide polymorphisms (SNPs) in the TUBB3 and cytochrome

	P450 gene The SNPs of TUBB3 and cytochrome P450 gene in peripheral blood cells would be measured by TaqMan OpenArray.
	Safety Endpoint: Throughout the study for both treatment arms, safety would be assessed by monitoring and recording all adverse events (AEs), serious adverse events (SAEs), laboratory parameters, vital signs, electrocardiograms (ECGs), ECOG scores, and physical and neurological examination results.
Statistical Methods	**Analysis Sets** The Full Analysis Set (Intent-to-treat [ITT] Analysis Set) included all subjects who were randomized. This would be the primary analysis set for all efficacy evaluations. The Per Protocol Analysis Set included those subjects who received at least one dose of eribulin or vinorelbine, had no major protocol violations, and had both Baseline and at least one post-Baseline tumor assessment, or those who died within 104 days after randomization in the absence of post-Baseline tumor assessment. This would be the secondary analysis set for efficacy evaluations. The Safety Analysis Set included all subjects who were randomized and received at least one dose of eribulin or vinorelbine and had at least one post-Baseline safety evaluation. Pharmacokinetics Analysis Set included those subjects selected for PK analyses. For each subject in the PK Analysis Set, there must be sufficient pharmacokinetic data to derive at least one pharmacokinetic parameter after eribulin administration. **Analysis of Primary Efficacy Endpoints** Unless otherwise specified, independent radiologic review according to RECIST 1.1 would be primarily used for all statistical analysis on tumor assessment related endpoints. The investigator’s assessments data would be secondarily used. All stratified analyses would be based on the stratification factor (receptor status and prior chemotherapy numbers) at randomization recorded in IWRS data primarily. The stratified analyses based on clinical data would also be

	performed as sensitivity analysis. The unstratified analysis without any stratification factors would also be performed as supportive. **Progression-Free Survival （PFS）** The PFS curves of eribulin and vinorelbine arms would be estimated using the Kaplan-Meier (K-M) method. The 2-sided 95% confidence intervals of median and quartiles for PFS would be provided with Greenwood formula and log-log transformation. The difference between the two groups for PFS would be evaluated using stratified Log-rank test with receptor status and prior chemotherapy numbers. The hazard ratio and 95% CIs of PFS would be estimated using Cox Proportional hazard model with receptor status and prior chemotherapy numbers as strata. Summaries of PFS, the hazard ratio and 95% CIs between the two groups for PFS would be provided in tables and forest plots for the subgroups of interest, e.g. receptor status, prior chemotherapy numbers, etc. Additional subgroups would be specified in the SAP. **Analysis of Secondary Efficacy Endpoints** **Overall Survival（OS）** The OS curves of eribulin and vinorelbine arms would be estimated using the K-M method. The two-sided 95% confidence intervals of median and quartiles for OS would be provided with Greenwood formula and log-log transformation. The difference between the two groups for OS would be evaluated using same statistical methods for PFS. Subjects who were lost to follow-up, who withdraw consent or whose death was not confirmed would be censored at the last date the subject was known to be alive. Subjects who were still alive at data cut-off would be censored at the cut-off date. **Objective response rate (ORR)** Best overall response and objective response rate (ORR) based on independent radiologic review would be summarized by treatment group. The ORR for each treatment arm along with exact 95% confidence interval (Clopper-Pearson) would be calculated. The difference between the two groups for ORR would be evaluated using Cochran-Mantel-Haenszel (CMH) test stratified by receptor status and prior chemotherapy numbers. The odds ratio and its 95% CIs (asymptotic normal

	approximation) in ORR would also be calculated using stratified CMH method by receptor status and prior chemotherapy numbers. If tumor assessment of a subject cannot be confirmed through RECIST 1.1 (such as early withdrawal or scans that cannot be evaluated), it should be considered as unresponsive. **Duration of response** The Duration of Response would be summarized by treatment arm with the K-M method for the subset of subjects who have best overall response of CR or PR. The K-M estimate for each group would be plotted over time along with the number of subjects at risk. The estimates of median and quartiles would be provided with their 2-sided 95% CIs using Greenwood formula and log-log transformation. **Analysis of exploratory Variables** **Clinical Benefit Rate（CBR）** The difference between the two groups for CBR would be evaluated using the same statistical methods for ORR and the CBR for each treatment arm along with exact 95% confidence interval (Clopper-Pearson) would be calculated. **Disease Control Rate(DCR）** The difference between the two groups for DCR would be evaluated using the same statistical methods for ORR and the DCR for each treatment arm along with exact 95% confidence interval (Clopper-Pearson) would be calculated. **Durable Stable Disease** The dSD would be summarized by treatment group. **Time to Treatment Failure (TTF)** The difference between the two groups for TTF would be evaluated using same statistical methods for PFS. Subjects who were still on treatment at time of database cutoff were censored at cutoff date. Subjects who had not received at least one dose of study treatment were censored at the date of randomization. The date of treatment failure was defined as the date of completion/discontinuation of study treatment, or start date of new anticancer treatment, whichever occurs first.

Analysis of Safety

Summary statistics for adverse events, laboratory parameters, and other safety parameters would be provided for the Safety Analysis Set.

Descriptive summary statistics (e.g., mean, standard deviation, median, minimum, and maximum) of the laboratory results, vital signs and electrocardiogram parameters, and changes from baseline measurements would be evaluated by treatment group.

Analysis of Pharmacokinetics

The following PK parameters would be calculated to evaluate pharmacokinetic profiles of Day1 and Day 8:

Maximum observed plasma concentration (C_{max}), time at which the highest drug concentration occurs (t_{max}), area under the plasma concentration-time curve (AUC), terminal phase rate constant (λ_Z), terminal elimination phase half-life ($t_{1/2}$), distribution volume at steady-state (V_{ss}), total clearance (CL)

Other Analysis

The association between the efficacy of eribulin or vinorelbine and βIII-tubulin (TUBB3) expression in tumor tissue would be examined in the subjects who were in the Full Analysis Set having results the expression of TUBB3.
The association between the efficacy of eribulin or vinorelbine and single nucleotide polymorphisms (SNPs) of TUBB3 and cytochrome P450 gene in peripheral blood cells would be examined in the subjects who were in the Full Analysis Set. All analyses in terms of these measurements would be documented in a separate report.

Sample Size Rationale

The sample size estimate was based on the primary endpoint, PFS. Two months was assumed for the median PFS of vinorelbine and 0.75 was assumed for the hazard ratio for eribulin versus vinorelbine based on the sponsor's prior experience with eribulin. The type I error rate was set at 2-sided 0.05 and the power was set at 80%.

Based on the above assumptions, approximately 440 subjects would be randomized to eribulin or vinorelbine (220 subjects in each arm). A total of approximately 380 progression events or deaths prior to disease progression were required for the final analysis of PFS. The 380 progression events or deaths were estimated to occur approximately 24 months (18 months enrollment period and 6 months follow-up period) after the start of the randomization phase. Taking consideration of approximately 10% drop-out rate, approximately 440 subjects would be enrolled and randomized.

	The required number of subjects to be randomized would be re-assessed on an ongoing basis. If it became apparent that the assumption of drop-out rate was inaccurate then the number of randomized subjects might be adjusted accordingly. At the time of the re-assessment, the pooled sample of treatment group suggested that drop-out rate was higher than the above original assumption. Therefore the original sample size of 440 subjects was increased up to approximately 530 subjects (265 in each arm) in order to ensure achievement of the target number of 380 events based on independent radiologic review within the reasonable time frame. **Interim Analysis** No interim efficacy analysis was planned.
Results and Discussion	**Results of Efficacy** **<u>Primary Efficacy Endpoints</u>** **Progression-Free Survival (PFS)** The primary efficacy analysis of this trial was conducted for the Progression-Free Survival (PFS) based on the independent radiologic review of the subjects from full analysis set (FAS), when the target number of 380 PFS events among the two treatment groups had been observed. The median PFSs of Eribulin Group and Vinorelbine Group were 2.8 months (95% CI:2.8, 4.1) and 2.8 months (95% CI:2.7,2.8), respectively. The mean PFSs of Eribulin Group and Vinorelbine Group were 4.4 months (95% CI:3.9, 4.9) and 3.7 months (95% CI:3.3, 4.2), respectively. The hazard ratio (Eribulin/Vinorelbine) was 0.80 (95% CI:0.65，0.98), the P value of stratified Log-rank test based on receptor status and numbers of prior chemotherapy was 0.036, and the P value of unstratified log-rank test was 0.031, and there was statistical significant difference for PFS between the two groups. The above results indicated that the efficacy of eribulin was superior to vinorelbine. The results of the primary efficacy analysis were fully supported by the results obtained in the analysis on the Per Protocol Analysis Set. The results of almost all planned sensitivity analyses and subgroup analyses (Receptor status, Prior chemotherapy numbers, Age group, ECOG performance status, Her2/neu status, ER status, PR status, HR status, Triple negative, Number of organs involved, Number of prior chemotherapy regimens for treatment of locally advanced or metastatic disease, Prior vinorelbine, Refractory to taxanes, Dose escalation of study drug) were consistent with the primary PFS analyses, which showed favorable outcomes

for Eribulin compared with Vinorelbine in the hazard ratios for PFS.

Tumor assessment was conducted every six week. The sensitivity analysis considering the potential imbalance in measurement interval for the radiology assessments did not impact on PFS result of the primary analysis.

Secondary Efficacy Endpoints

(1) Overall Survival（OS）

The median OSs of Eribulin Group and Vinorelbine Group were 13.4 months (95% CI:11.5,16.2) and 12.5 months (95% CI:10.6,16.6), respectively. The hazard ratio (Eribulin/Vinorelbine) was 1.03 (95% CI:0.80,1.31) , the P value of stratified Log-rank test with receptor status and prior chemotherapy numbers was 0.838, and there was no statistical significant difference for OS between the two groups.

This study was not powered to detect significant difference between the two groups for OS. At the time of primary analysis the amount of death events may not be sufficient to provide mature OS results.

(2) Objective Response Rate (ORR)

The ORRs of Eribulin Group and Vinorelbine Group were 30.7% (95% CI:25.2%，36.6%) and 16.9% (95% CI:12.6%，22.0%), respectively. The P value of CMH test with receptor status and prior chemotherapy numbers was <0.001, the odds ratio (Eribulin/Vinorelbine) was 2.17 (95% CI:1.44,3.29). The above results indicated that the efficacy of eribulin was superior to vinorelbine for ORR.

The results of all planned subgroup analyses were consistent with the above results, which showed favorable outcomes for Eribulin compared with Vinorelbine in the odds ratios for ORR. The overall results in ORR analyses were corroborative of the results of the primary PFS analysis.

(3) Duration of Response

The median duration of response of Eribulin Group and Vinorelbine Group were 89.0 days (95% CI:85.0,136.0) and 86.0 days (95% CI:71.0,115.0), respectively.

Exploratory Endpoints

(1) Clinical Benefit Rate（CBR）

The CBRs of Eribulin Group and Vinorelbine Group were 38.6% (95% CI:32.7%,44.8%) and 23.3% (95% CI:18.4%,28.9%), respectively. The P value of CMH test with receptor status and prior chemotherapy numbers was <0.001,

	the odds ratio (Eribulin/Vinorelbine) was 2.06 (95% CI:1.42,3.01). There was statistical significance for CBR between the two groups. The above results indicated that the efficacy of eribulin was superior to vinorelbine for CBR. **(2) Disease Control Rate（DCR）** The DCRs of Eribulin Group and Vinorelbine Group were 49.2% (95% CI:43.1%,55.4%) and 33.1% (95% CI:27.5%,39.1%), respectively. The P value of CMH test with receptor status and prior chemotherapy numbers was <0.001, the odds ratio (Eribulin/Vinorel- bine) was 1.95 (95% CI:1.38,2.78). There was statistical significance for DCR between the two groups. The above results indicated that the efficacy of eribulin was superior to vinorelbine for DCR. **(3)Durable Stable Disease（dSD）Rate** The dSD rate of Eribulin Group was 8.0% and the dSD rate of Vinorelbine Group 6.4%, respectively. **(4) Time to Treatment Failure (TTF)** The median TTFs of Eribulin Group and Vinorelbine Group were 3.2 months (95% CI:2.9,4.0) and 2.7 months (95% CI:2.1,2.8), respectively. The hazard ratio(Eribulin/Vinorelbine) was 0.72 (95% CI:0.60,0.86), the P value of stratified Log-rank test with receptor status and prior chemotherapy numbers was <0.001, and there was statistical significance for TTF between the two groups. The above results indicated that eribulin was superior to vinorelbine for TTF. **Pharmacokinetic Results** After eribulin was administered intravenously over 2 to 5 minutes, eribulin was eliminated from plasma bi- or tri-phasically. Pharmacokinetic parameters obtained after administration on Day 8 were similar to those after administration on Day 1 in both eribulin regimens. **Safety Results**: **Adverse Events (AEs)** In this study, characteristics of AEs with eribulin were consistent with the results of previous studies on eribulin. There were 517 cases of treatment emergent adverse event (TEAE), with incidence of 99.2%, among which, 261 cases TEAE occurred in Eribulin Group with incidence of 98.9%, and 256 cases occurred in Vinorelbine Group with incidence of 99.6%. There were 261 cases of study drug-related TEAE occurred in Eribulin Group, with incidence being 98.9%, and 254 cases in Vinorelbine Group, with incidence of 98.8%. The most common TEAE in Eribulin Group was white blood cell count decreased and neutrophil count decreased and the most common study drug-related TEAE in Eribulin groups was also white blood cell count decreased and

	neutrophil count decreased. The most common TEAE in Vinorelbine Group was white blood cell count decreased and neutrophil count decreased, and the most common study drug-related TEAE in Vinorelbine groups was also white blood cell count decreased and neutrophil count decreased. In the eribulin group and the vinorelbine group, development of Grade 3/4 neutrophil count decreased occurred in 79.9% and 77.0% of patients, respectively. The incidence of Grade 3/4 neutropenia in the eribulin group and vinorelbine group were 2.3% and 3.1%, respectively. The incidence of Grade 3/4 febrile neutropenia occurred in the eribulin group and the vinorelbine group were 2.7% and 1.2%, respectively. In the eribulin group, TEAE of neuropathy peripheral and peripheral sensory neuropathy were reported for 0.8% and 0.8 % of patients, respectively, and Grade 3/4 of these TEAEs were not reported. In the vinorelbine group, development of neuropathy peripheral and peripheral sensory neuropathy occurred in 0.8% and 1.2% of patients, respectively, and the incidence of Grade 3/4 of these TEAEs were 0.4% and 0.4%, respectively. TEAEs of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 and above were the most common AEs reported in both two groups. **Serious Adverse Events** There were 25 cases serious TEAE in Eribulin Group and incidence was 9.5%; while, 32 cases in Vinorelbine Group and incidence 12.5%. There 16 cases study drug-related serious TEAE in Eribulin Group, and incidence was 6.1%; while, 20 cases in Vinorelbine Group, and incidence 7.8%. The most common serious TEAE in Eribulin Group was febrile neutropenia and the most common study drug-related TEAE in Eribulin Group was also febrile neutropenia. The most common serious TEAE in Vinorelbine Group was leukopenia. The most common study drug-related TEAE in Vinorelbine Group was leukopenia. **Death** Up to the database cut-off date, there were 6 cases with TEAE with fatal outcome in Eribulin Group and 4 cases in Vinorelbine Group, respectively. The main cause of death in both groups was progression of disease. **Adverse Events leading to discontinuation use of study drug** There were 19 cases of TEAE which lead discontinuation use of study drug in Eribulin Group, the incidence was 7.2%; while, 36 cases in Vinorelbine Group, incidence 14.0%. There were 16 cases study drug-related TEAE leading to discontinuation use of study drug in Eribulin Group and 30 cases in Vinorelbine Group, respectively; The incidence was 6.1% in Eribulin Group and 11.7% in Vinorelbine Group, respectively. The most common TEAE leading to discontinuation use of study drug in Eribulin Group was neutrophil count decreased and the most common study drug-related TEAE leading to discontinuation use of study drug in Eribulin groups was also the neutrophil

	count decreased. The most common TEAE leading to discontinuation use of study drug in Vinorelbine Group was neutrophil count decreased and asthenia, and the most common study drug-related TEAE leading to discontinuation use of study drug in Vinorelbine groups was also neutrophil count decreased and asthenia.
Conclusion	Eribulin injection had good clinical efficacy in the treatment of Chinese female patients with Locally Recurrent or Metastatic Breast Cancer. Compared with vinorelbine, eribulin could significantly prolong PFS. The other endpoints of ORR, TTF, CBR and DCR were consistent with the primary endpoint. Meanwhile, the results of eribulin safety observation showed that in the background of advanced disease, observed safety characteristics of eribulin as chemo- therapy drug were acceptable. The incidence of grade 3/4 neutrophil count decreased was similar to the one of previous eribulin study conducted in Japan. These safety characteristics were consistent with the results observed in previous studies. In conclusion, there were good efficacy and safety of eribulin injection in the treatment of Chinese female patients with Locally Recurrent or Metastatic Breast Cancer.
Report Date	27 October 2017