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1. TITLE PAGE

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CLINICAL STUDY PROTOCOL

A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes

Study Number:	**E7389-G000-301**
Phase:	**III**
Investigational Product:	**E7389**
EudraCT Number:	**2005-004009-26**
Indication:	**Locally Advanced or Metastatic Breast Cancer after Prior Chemotherapy with Anthracyclines and Taxanes**

Original Protocol	17 November 2005
Amendment 1	14 December 2005
Amendment 2	02 March 2006
Amendment 3	11 May 2006
Amendment 4	05 December 2006
Amendment 5	31 October 2007
Amendment 6	06 March 2008
Amendment 7	03 March 2009

SIGNATURE PAGE

Study Title: A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes

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INVESTIGATOR SIGNATURE

I have read the protocol and appendices. I understand the contents and intend to comply fully with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal authorization by Eisai in the form of a protocol amendment.

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PROTOCOL NUMBER: E7389-G000-301

Title of Protocol: A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes

Eisai Protocol Review Committee Date of Approval: 17 November 2005 (Protocol)
14 December 2005 (Amendment 1)
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06 March 2008 (Amendment 6)

IND Number: 67,193

EudraCT Number: 2005-004009-26

Number of Centers: Approximately 210 centers

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INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE:

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SPONSORS:

The Sponsors for this study are Eisai Medical Research Inc for North and South America; and Eisai Ltd for Europe and Rest of World.

2. PROTOCOL SYNOPSIS

Eisai Study Number:	**E7389-G000-301**
Study Title:	A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes
Objectives:	The primary objective of this study is to compare the efficacy of E7389 versus capecitabine monotherapy, in terms of Overall Survival and Progression-Free Survival in patients with locally advanced or metastatic breast cancer Secondary objectives are to assess: • Quality of Life measured using the EORTC questionnaire • Objective Tumor Response Rate as measured using RECIST criteria • Duration of Response • One, Two and Three year Survival • Tumor Related Symptom Assessments measured by pain intensity (VAS), and analgesic consumption • Safety Parameters (adverse events, laboratory parameters, concomitant medication, and study drug exposure) • Pharmacokinetic/pharmacodynamic relationships in a population pharmacokinetic investigation in a minimum of 200 patients in the E7389 arm
Study Phase:	III
Study Design:	Multicenter, open-label, two-parallel-arm randomized study
Number of Centers:	Approximately 210 centers
Number of Patients:	A maximum of 1100 patients (550 per treatment arm)
Type of Patients:	Patients with locally advanced or metastatic breast cancer who have received up to three prior chemotherapy regimens, and no more than two prior regimens for advanced disease. The regimens must have contained an anthracycline and a taxane component, either in the (neo)adjuvant setting or for locally advanced or metastatic disease. Patients must have documented evidence of progression during or after their most recent anti-cancer therapy. Patients with a known HER-2/neu over-expressing status may also have been treated with trastuzumab in centers where this treatment is available. Patients with estrogen and/or progesterone receptor positive tumors may have been treated with hormonal therapy.

Eisai Study Number:	E7389-G000-301
Treatments:	E7389 1.4 mg/m^2 IV infusion given over 2-5 minutes on Days 1 and 8 every 21 days; **or** Capecitabine 2.5g/m^2/day administered orally twice daily in two equal doses on Days 1 to 14 every 21 days.
Study Procedures:	All Screening procedures except for the Baseline tumor assessment will be conducted within 14 days prior to start of study treatment. Baseline tumor assessments, consisting of radiologic evaluation of the chest, abdomen, pelvis, and any other areas of suspected disease as well as photographs of any skin lesions to be followed as target lesions, will be performed within 28 days prior to start of treatment. A radio-isotope bone scan (with 99m technetium-labelled polyphosphonate scintigraphy) will be performed within six weeks prior to start of treatment. An ECG will be taken at Baseline, end of Cycle 2 and at the study termination visit. Clinical examination and laboratory screens will be performed weekly for the first two cycles, and then on Days 1 and 8 of every further cycle (lab assessments must be performed within 72 hours prior to Cycle 1, Day 1, and within 1 day prior to Day 1 for all subsequent cycles and Day 8 for all cycles). If medically indicated, the assessments will be performed more frequently. Adverse events (AEs) and concomitant medications will be assessed throughout the study. Tumor measurements will be performed every two cycles starting at the end of Cycle 2. Additional tumor assessments will be performed if there is symptomatic evidence suggesting the possibility of disease progression on clinical examination. Post-screening bone scans will be performed every six cycles starting at the end of Cycle 6. Patients will complete the EORTC quality of life questionnaire at baseline and at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months after start of treatment. Patients will record pain scores on a 1-100 mm visual analogue scale weekly and analgesic consumption will be recorded throughout treatment. Patients should attend a study termination visit within 30 days after the last dose of study medication and will then be followed-up either by telephone or clinic visit every 12 weeks from the last tumor assessment to determine disease status and/or survival.

Eisai Study Number:	E7389-G000-301
Pharmacokinetic Assessments	Pharmacokinetic (PK) sampling will occur in the E7389 arm only, in a minimum of 200 patients. Population analysis with sparse sampling collection schedule will be used to characterize the PK profile of E7389. Attempts will be made to identify the covariates that affect drug behavior, or those that explain variability in a heterogeneous patient population. Plasma concentrations of E7389 will be determined using a fully validated LC/MS/MS method. Prior to the analysis of study samples, the assay sensitivity, specificity, linearity and reproducibility will be documented. The PK of E7389 will be assessed during the first cycle of treatment only. A total of four samples will be taken from each participating patient.
Study Duration:	Patients will remain on study treatment until one or more of the following occur: • Progressive Disease by clinical evaluation or as documented by RECIST Criteria • Losing clinical benefit because of undue toxicity • The patient withdraws consent • The investigator concludes that further therapy is not in the best interest of the patient • Presence of other medical conditions that prohibit continuation with therapy • Pregnancy • Failure of patient to comply with study procedures that compromise safety, despite repeated efforts of the investigator to contact the patient, with complete documentation of the circumstances • A delay of more than 14 days in starting the next cycle due to toxicities, or the presence of residual toxicities that in the opinion of the investigator prohibit further administration of treatment • Presence of new medical information that warrants the termination of the study • Termination of the study by the Sponsor
Efficacy Assessments:	Overall survival, progression free survival, objective tumor response according to RECIST criteria, duration of response
Safety Assessments:	Adverse events, concomitant medications, laboratory assessments and electrocardiograms

Eisai Study Number:	E7389-G000-301
Other Assessments:	Quality of Life measured using the EORTC Quality of Life assessment Tool (QLQ-C30) plus breast module BR23; Tumor-Related Symptom Assessments measured by pain intensity (VAS) and analgesic consumption.
Statistics:	The study will be declared positive after achievement of any of the following outcomes: 1. First interim analysis after 453 deaths: Overall survival of E7389 is statistically significantly better compared to capecitabine ($p \leq 0.002$), 2. Second interim analysis after 603 deaths: Overall survival of E7389 is statistically significantly better compared to capecitabine ($p \leq 0.0081$), 3. Final analysis after 905 deaths: Overall survival of E7389 is statistically significantly better compared to capecitabine ($p \leq 0.0372$), 4. Final analysis after 905 deaths: Overall survival hazard ratio (E7389/capecitabine) is < 1 ***and*** progression free survival of E7389 is statistically significantly better compared to capecitabine ($p \leq 0.01$). Decisions will be based on two-sided, stratified log-rank tests with HER2/neu status and geographic region as strata. Overall Survival (OS) is measured from the date of randomization until the date of death from any cause. Overall survival will be compared between the two groups using a two-sided stratified log-rank at a nominal level of 0.0372 as the primary analysis. Hypothesis to be tested are: $H_0: S_{E7389} = S_{Capecitabine}$ $H_a: S_{E7389} \neq S_{Capecitabine}$ Where, S is the survival distribution of overall survival. The p-value from two-sided stratified log-rank test will be presented. In subsequent analyses, treatment effect estimates will be summarized using 95% confidence intervals. Median and 95% CI will be provided for each treatment group. Kaplan-Meier plots will be provided for overall survival. Hazard ratio (E7389/Capecitabine) will be computed together with the two-sided 95% CI using stratified Cox regression model with treatment as a factor and HER2/neu status and geographic region as strata in the model for the ITT population.

Eisai Study Number:	E7389-G000-301
	Progression-Free Survival (PFS) will be compared between the two treatment groups using a two-sided 0.01 level stratified log-rank test.
Statistics (continued):	Quality of Life (QoL) will be assessed using the EORTC quality of life questionnaire. The difference in QoL scores for questions 29 and 30 at week six will be the primary interest. Hence at week 6, the treatment difference will be compared using a Wilcoxon Rank-Sum test separately for the two questions at 0.025 level. Objective Response Rate (ORR) will be compared between the two groups using a Fisher's exact test. For the duration of response, Kaplan-Meier plots will be provided along with the median and the 95% confidence interval. Tumor response data utilized for primary analysis of PFS, ORR and duration of response will be obtained from an independent review of the imaging scans. In addition, these analyses will be performed using the investigators' determination of response. Response will be assessed according to RECIST criteria. Complete description of the independent review assessment will be detailed in an Independent Imaging Review Charter. Tumor-Related Symptom Assessments will be based on change from Baseline in pain intensity and analgesic use. Descriptive statistics will be provided at each assessment. Patients will be classified as improved, no change, or worsened. A patient will be considered a responder if patient has improved in both parameters (intensity and analgesic use). Responders in the two groups will be compared using a chi-square test. Summary statistics for adverse events, laboratory parameters, and other safety parameters will be provided for the safety population. Two interim analyses will be performed, one analysis after half and a second after two thirds of the deaths have been observed.

2.2 PROTOCOL FLOWCHART

Assessments	Screening	Treatment Cycle (days)			Study Termination
	Days −14 to 0	Day 1	Day 8	Day 15[b]	Within 30 Days of final treatment
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Demographic Data	X				
Medical/Surgical History	X				
Tumor Assessments (RECIST)[a]	X			X	X
ECOG Performance Status	X	X			X
Physical Examination[c]	X	X	X	X	X
Vital Signs, Height and Weight[d]	X	X[d]	X[d]	X[d]	X[d]
12-Lead ECG[e]	X			X[e]	X
Pregnancy Test (if applicable)[f]	X	X			
Hematology, Chemistry	X	X[g,h]	X[g,h]	X[g,h]	X
Urinalysis	X	X[g]			X
EORTC QoL Questionnaire		X[i]			
Pain Assessment (VAS)		X[j]	X	X	X
Prior and Concomitant Medications and Procedures	X	Throughout			X
Adverse Events	X	Throughout			X
E7389 Administration[k]		X[l]	X[l]		
PK Sampling[m]		X			
OR					
Capecitabine Administration[k]		Days 1-14			

a. Baseline tumor assessments, consisting of CT or MRI scans of the chest, abdomen and pelvis and any other areas of suspected disease, as well as photographs of skin lesions being measured as target lesions should be performed within 28 days prior to starting study treatment. The chest and abdomen plus any other areas where disease was found at Baseline will then be scanned/photographed every second cycle (starting Cycle 2) between Days 15 and 21, or sooner if there is evidence of progressive disease. Any new areas of suspected disease identified at these time-points should also be scanned/photographed. If patients remain on study for more than 12 cycles after starting treatment, the assessments described above will then be performed every three cycles until PD. A radionuclide bone scan using 99m technetium-labelled polyphosphonate scintigraphy should be performed within six weeks before start of study treatment, and should be repeated every sixth cycle (starting Cycle 6) between Day 15 of the sixth cycle and Day 7 of the following cycle. If patients discontinue from treatment without PD, tumor assessments (except bone scans) should be performed at study termination (within 30 days of

last study drug administration) and then every three months until PD or start of another anti-cancer therapy. Radionuclide bone scans for these patients should be performed every six months following study termination until PD or start of another anti-cancer therapy.

b. Day 15 assessments (apart from VAS on Day 15 and tumor assessments performed between Day 15 and Day 21) will only be performed for the first two cycles, unless clinically indicated.

c. A complete physical examination will be done at Screening, Day 1 of each cycle and at Study Termination. A symptom directed physical exam will be performed on Day 8 of every cycle, as well as on Day 15 of the first two cycles (thereafter on Day 15 of subsequent cycles only if clinically indicated).

d. Height will be measured at screening only. Weight will be measured on Day 1 pre-dose of each cycle. Vital signs will be performed on Day 1 and Day 8 pre-dose of all cycles and on Day 15 during the first two cycles only, unless clinically indicated.

e. ECG will be taken at baseline, end of Cycle 2 and termination visit only.

f Urine or serum pregnancy test at screening and pre-dose Day 1, first cycle only. Assessments scheduled on Day 1 Cycle 1 may be performed within 72 hours prior to Day 1 Cycle 1

g Laboratory assessments must be reviewed prior to drug administration. Assessments scheduled on Day 1 of Cycle 1 may be performed within 72 hours prior to the Day 1 of Cycle 1 visit. Assessments scheduled on Day 1 of all other cycles, Day 8 and Day 15 may be performed within 1 day prior to scheduled visit

h. If neutropenia or thrombocytopenia ≥ Grade 3, repeat complete blood count with differential and AE assessment as per standard of care until improvement to < Grade 3

i EORTC QoL questionnaires will be competed at Baseline (within seven days of Day 1 Cycle 1), thereafter at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months after start of treatment, before drug administration and before any tumor assessments. Questionnaires should continue to be completed at the scheduled time-points (including beyond study termination), until the patient has progressive disease or starts a different course of anti-tumor treatment.

j. Baseline pain assessment (VAS) will be completed within seven days prior to Day 1 Cycle 1

k. Patients will be randomized to receive E7389 or capecitabine monotherapy

l. Therapy will be administered on Days 1 and 8 every 21 days, continuing until reasons for discontinuation specified in section 8.4 are fulfilled. Patients who demonstrate clinical benefit can continue treatment for as long as clinical benefit is sustained. Treatment will be administered on Days 1 and 8 whenever possible. If holidays or personal schedules make administration on Days 1 or 8 impossible, then administration will be as close to the targeted date as possible. Treatment on Day 1 may be given up to one day earlier or two weeks later. Treatment on Day 8 may be given one day earlier or up to one week later. If Day 8 is delayed beyond Day 15, the second administration in this cycle will be omitted, and treatment will resume as scheduled on Day 1 of the next cycle. Regardless of the time of administration, toxicity from previous treatment must be within acceptable ranges as described in section 9.6.1.

m. PK sampling will be performed in E7389 arm only; for a minimum of 200 patients. For those patients participating in PK sampling, PK sampling time-points (after start of infusion) are 5-10, 15-30, 30-60, and 60-90 minutes, and 2-4, 4-8, 10-24, 48, 72, and 96-120 hours. Participating patients will be randomized to a schedule containing 4 time-points per patient.

3. TABLE OF CONTENTS

1. TITLE PAGE 1
SIGNATURE PAGE 3
2. PROTOCOL SYNOPSIS 10
2.2 PROTOCOL FLOWCHART 15
3. TABLE OF CONTENTS 18
3.1 LIST OF TABLES 22
3.2 LIST OF FIGURES 22
4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS 23
5. INTRODUCTION 26
5.1 BACKGROUND 26
5.2 E7389 27
5.2.1 Nonclinical Pharmacology 27
5.2.2 Pharmacokinetics/Metabolism 28
5.2.3 Toxicology 30
5.2.4 Clinical Studies 30
5.3 RATIONALE 31
6. STUDY OBJECTIVES 33
7. INVESTIGATIONAL PLAN 34
7.1 OVERALL STUDY DESIGN AND PLAN – DESCRIPTION 34
7.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS 34
7.3 DEFINITION OF END OF STUDY 34
8. SELECTION OF STUDY POPULATION 35
8.1 NUMBER OF PATIENTS 35
8.2 INCLUSION CRITERIA 35
8.3 EXCLUSION CRITERIA 36
8.4 REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT 38
9. TREATMENTS 39
9.1 IDENTITY OF INVESTIGATIONAL PRODUCT(S): E7389 39
9.1.1 Drug Substance 39
9.1.2 Physical and Chemical Characteristics 40
9.2 COMPARATOR: CAPECITABINE 40
9.3 LABELING, PACKAGING AND STORAGE: E7389 40

9.3.1 Labeling 41
9.3.1.1 USA labeling requirements 41
9.3.1.2 Canadian labeling requirements 41
9.3.1.3 European labeling requirements 41
9.3.2 Storage 41
9.4 LABELING, PACKAGING AND STORAGE: CAPECITABINE 42
9.5 DRUG SUPPLIES 42
9.6 ADMINISTRATION OF TREATMENTS 43
9.6.1 E7389 43
9.6.1.1 Administration schedule 43
9.6.1.2 Dose modification 44
9.6.1.3 Treatment in subsequent cycles 44
9.6.1.4 Dose modification on Day 1 44
9.6.1.5 Dose modification or reschedule on Day 8 45
9.6.1.6 Subsequent dose modifications 45
9.6.2 Capecitabine 45
9.6.2.1 Dose modifications 45
9.7 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS 46
9.8 SELECTION OF DOSES IN THE STUDY 46
9.9 BLINDING 47
9.10 PRIOR AND CONCOMITANT THERAPY 47
9.10.1 Concomitant treatments permitted 47
9.10.2 Concomitant treatments not permitted 48
10. ASSESSMENTS 49
10.1 SAFETY 49
10.1.1 Physical Examination 49
10.1.2 Vital Signs, Height and Weight 49
10.1.3 Electrocardiograms 49
10.1.4 Laboratory Assessments 49
10.1.4.1 Hematology 49
10.1.4.2 Clinical Chemistry 50
10.1.4.3 Urinalysis 50
10.1.4.4 Pregnancy test 50
10.1.5 Data Monitoring Board 50
10.2 EFFICACY 51
10.2.1 Tumor Assessments 51
10.2.2 Target and non-target lesions 52
10.2.2.1 Measurable Disease 52
10.2.2.2 Clinically Evaluable Disease 52
10.2.3 Independent blinded review 53
10.3 CLINICAL BENEFIT ENDPOINTS 53

10.3.1 Pain intensity 53
10.3.2 Analgesic consumption 53
10.3.3 ECOG performance status 53
10.3.4 Quality of Life (EORTC questionnaire) 53
10.4 PHARMACOKINETICS 54
11. SCHEDULE OF ASSESSMENTS 56
11.1 SCREENING AND ENROLLMENT 56
11.1.1 Screening 56
11.1.2 Randomization 56
11.2 TREATMENT PERIOD 57
11.2.1 Day 1 of Each 21-Day Cycle 57
11.2.2 Days 2-7 of Each 21-Day Cycle (capecitabine treatment arm only) 58
11.2.3 Day 8 of Each 21-Day Cycle 58
11.2.4 Days 9-14 of Each 21-Day Cycle (capecitabine treatment arm only) 58
11.2.5 Day 15 of Each 21-Day Cycle 58
11.2.6 Days 15-21 every second cycle 59
11.2.7 Day 15 of every sixth cycle – Day 7 of the following cycle 59
11.2.8 Study Termination (0-30 days after final dose, or at discontinuation) 59
11.3 FOLLOW-UP 60
12. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND REPORTING 61
12.1 ADVERSE EVENTS, SEVERITY AND RELATIONSHIP 61
12.1.1 Assessing Severity of Adverse Events 61
12.1.2 Assessing Relationship to Study Treatment 62
12.1.3 Classification of Causality 62
12.2 SERIOUS ADVERSE EVENTS 62
12.2.1 Definition of Serious Adverse Events 62
12.2.2 Reporting of Serious Adverse Events 63
12.3 PREGNANCY REPORTING 64
13. STATISTICAL METHODS 66
13.1 DETERMINATION OF SAMPLE SIZE 66
13.2 STATISTICAL PLAN 66
13.2.1 Primary Efficacy Endpoints 66
13.2.1.1 Overall Survival (OS) 66
13.2.1.2 Progression-Free Survival (PFS) 66
13.2.2 Secondary Endpoints 66

13.2.3 Definition of study populations for analysis 67
13.3 Analysis of Baseline and Demographic Variables 67
13.4 Efficacy Analyses 67
13.4.1 Decision Rules and Adjustment of Alpha for Primary Endpoints 67
13.4.2 Analysis of Primary Efficacy Endpoints 68
13.4.2.1 Overall Survival 68
13.4.2.2 Progression Free Survival 69
13.4.3 Analysis of Secondary Efficacy Endpoints 70
13.5 Analysis Of Clinical Benefits Endpoints 71
13.5.1 Quality of Life (QoL) 71
13.5.2 Tumor-Related Symptom Assessments 72
13.6 Safety Analysis 72
13.6.1 Adverse Events 73
13.6.2 Deaths, Other Serious and Other Significant Adverse Events 73
13.6.3 Clinical Laboratory Parameters 73
13.6.4 Other Safety Parameters 73
13.6.5 Analysis of Pharmacokinetic Variables 73
13.7 Interim Analyses and Safety: Data Monitoring Board (DMB) 73
14. ETHICS 75
14.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB) 75
14.2 Ethical Conduct of the Study 75
14.3 Patient Information and Consent 75
15. TREATMENT COMPLIANCE 77
15.1 Drug Accountability Procedures 77
15.2 Receipt of Study Drugs 77
15.3 Handling of Study Drugs 77
15.4 Records of Study Drugs 78
16. STUDY MANAGEMENT AND ADMINISTRATION 79
16.1 Monitoring 79
16.2 Audit and Inspection 79
16.3 Source Documents 79
16.4 Case Report Forms 80
16.5 Investigator Site File 80
16.6 Premature Termination of the Study 81
16.7 Clinical Study Report 81

16.8 Patient Insurance and Indemnity 81
16.9 Amendments to the Protocol 81
16.10 Disclosure of Information and Results 82
16.11 Publication and Presentation Policy 82
16.12 Archiving and Data Retention 82
16.13 Data Protection 82
17. REFERENCES 84
18. APPENDICES 87
Appendix 1 World Medical Association Declaration of Helsinki
Appendix 2 US Consent for Use of Investigational New Drug (IND) on Human Subjects: Statement of Policy
Appendix 3 US Organization and Procedural Requirements for Institutional Review Boards: Statement of Policy
Appendix 4 Capecitabine Dose Calculation According to Body Surface Area
Appendix 5 Eastern Cooperative Oncology Group Performance Status Scale
Appendix 6 Cockcroft - Gault Formula for Calculated Creatinine Clearance
Appendix 7 EORTC QLQ-C30
Appendix 8 EORTC QLQ – BR23
Appendix 9 Visual Analogue Pain Scale
Appendix 10 Distribution of Active Bone Marrow in the Adult
Appendix 11 NYHA Cardio Grading
Appendix 12 RECIST Criteria Highlights

3.1 List of Tables

Table 1: Recommended Dose Modifications with Capecitabine Monotherapy 46
Table 2: Censoring Rules for Progression Free Survival 70
Table 3: Classifications for Post-Baseline Tumor-Related Symptom Assessments 72

3.2 List of Figures

Figure 1: Chemical Structure of E7389 39

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
β-hCG	Beta human chorionic gonadotropin
BSA	Body surface area
CI	Confidence interval
CNS	Central nervous system
C_{max}	Maximum observed plasma concentration
CR	Complete response
CRF	Case report form
CT	Computer tomography
CTC	Common toxicity criteria
CPK	Creatine phosphokinase
CYP	Cytochrome P-450 system
dL	Deciliter
DLT	Dose-limiting toxicity
DMB	Data Monitoring Board
DVT	Deep vein thrombosis
E7389	(11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-i]furo[2',3':5,6]pyrano[4,3-b][1,4]dioxacyclopentacosin-5(4*H*)-one, 2-[(2*S*)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*, 12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-, methanesulfonate salt)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGC	Eisai Global Clinical Development
EMR	Eisai Medical Research, Inc
EORTC	European Organization for Research on the Treatment of Cancer
ER	Estrogen Receptor
ESL	Eisai Ltd
EU	European Union
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyl transpeptidase
GLP	Good Laboratory Practices
GM-CSF	Granulocyte-macrophage colony-stimulating factor

Abbreviation	Definition
HalB	Halichondrin B
Hb	Hemoglobin
HCT	Hematocrit
HEENT	Head, ears, eyes, nose and throat
HER2/neu	Human Epidermal Growth Factor 2
hERG	Human EAG Related Gene
HIV	Human immunodeficiency virus
hr(s)	Hour(s)
HR	Hazard Ratio
IC_{50}	Inhibitory Concentration 50%
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
kg	Kilogram
L	Liter
LC/MS/MS	Liquid chromatography with mass spectrometry detection
LD	Longest diameter
LDH	Lactate Dehydrogenase
m^2	Meter squared
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
min	Minutes
mm	Millimeter
mmol	Millimole
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
N	Number
NaCl	Sodium chloride
NCI	National Cancer Institute
ng	Nanograms
NIH	National Institute of Health
nM	Nanomolar
NSCLC	Non-small Cell Lung Cancer
NYHA	New York Heart Association
ORR	Objective response rate
PD	Progressive disease
pH	Hydrogen ion concentration; negative base 10 logarithm of the hydrogen ion concentration; measure of the acidity or alkalinity of a solution
PI	Principal investigator
PK	Pharmacokinetic

Abbreviation	Definition
PR	Partial response OR Progesterone receptor, depending on context
PS	Performance status
PVC	Poly-vinyl chloride
QDx5	Daily times 5
Q4Dx3	Every 4 days times 3
Q7Dx3	Every 7 days times 3
QoL	Quality of Life
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
$t_{1/2}$	Half life
t_{max}	Time of maximum observed plasma concentration
TOI	Trial outcome index
TP	Thymidine phosphorylase
TTP	Time to progression
µg	Micrograms
µM	Micromolar
ULN	Upper limit of normal
US	Ultrasound
US	United States
VAS	Visual analog scale
V_d	Volume of distribution
V_{ss}	Volume of distribution at steady state
WBC	White blood cell

5. INTRODUCTION

5.1 Background

Worldwide, more than a million women are diagnosed with breast cancer every year, accounting for a tenth of all new cancers and 23% of all female cancer cases. Incidence rates vary considerably, with the highest rates in the developed world and the lowest rates in Africa and Asia. Around 361,000 cases occur each year in Europe and 210,000 in the USA. The lowest European rates are in Eastern and Southern Europe and the highest are in Denmark, Belgium, Sweden and the Netherlands. The estimated incidence of breast cancer in 2004 in the US was reported to be 217,440 with 40,580 deaths expected during that year.[1]

Approximately 15% of the new cases of breast cancer are diagnosed at an advanced stage, and depending on stage, grade and treatment modalities, 20-80% of all invasive breast cancer patients eventually need treatment for a relapse.[2] Combination chemotherapies for patients with locally advanced or metastatic disease are generally considered the standard of care,[3] although the benefit of combination therapy as compared to single agent therapy continues to be discussed. Combination therapies show statistically significant advantage for tumor response and time to progression, modest improvement in overall survival, but significantly higher toxicity, as compared to single agent therapies.[4] Combinations, including anthracyclines, doxorubicin, epirubicin or an analogue, mitoxantrone, have produced response rates of 40%-60%, and are considered the most efficacious first line chemotherapy for advanced breast cancer.[5] After the introduction of taxanes in the 1990s, due to their high efficacy, they rapidly became an important part of breast cancer treatment. A meta-analysis of 21 trials comparing taxane chemotherapy regimens to non-taxane combinations indeed indicates that taxanes improve overall survival, time to progression, and overall response rates in patients with metastatic breast cancer.[6] However, initial responses in general last between 8 and 14 months, and disease progression is inevitable.[2,7,8] Among patients treated with systemic chemotherapy at a single institution, 16.6% achieved complete responses, but only 3.1% remained in complete remission for more than five years.[2]

Capecitabine, is an orally bioavailable prodrug enzymatically converted by thymidine phosphorylase (TP) to fluorouracil at the tumor site. To enhance the salvage therapy of advanced breast cancer, capecitabine received an accelerated approval from the FDA in 1998. Approval was based on a single arm Phase II trial in 162 patients with metastatic breast cancer, treated with 2-3 prior regimens including paclitaxel, showing an overall response rate of 18.5%. The median time to progression was 3.1 months (CDER Application NDA 20-896). Capecitabine was subsequently approved by the EMEA in 2002 for second line treatment of breast cancer. A large multicenter Phase II trial demonstrated that capecitabine was active in patients with metastatic breast cancer, treated with two or three previous chemotherapies (25% CR+PR), including those refractory to both paclitaxel and anthracyclines.[9] Combination therapies utilizing capecitabine plus a taxane have also yielded promising activity (50% response rate).[1] In a more recent Phase III study, 462 patients with metastatic breast cancer, previously treated with anthracycline- and taxane-containing regimens, were

6. STUDY OBJECTIVES

Primary Objective

The primary objective of this study is to compare the efficacy of E7389 versus capecitabine monotherapy in terms of Overall Survival and Progression-Free Survival (PFS), in patients with locally advanced or metastatic breast cancer.

Patients must have been previously treated with regimens containing an anthracycline and a taxane component or a combination of both. In cases where it is known that the tumor over-expresses HER2/neu (see section 11.1.2), patients may have been treated with trastuzumab in centers where this treatment is available, and estrogen and/or progesterone receptor-expressing tumors may have been treated with hormonal therapy.

Secondary Objectives

- Assess and compare between the two treatment groups:
    - Quality of Life measured using the EORTC questionnaire
    - Objective Tumor Response Rate as measured using RECIST criteria[22]
    - Duration of Response
    - One, two and three year survival
    - Tumor Related Symptom Assessments measured by pain intensity (VAS) and analgesic consumption.
    - Safety parameters (adverse events, laboratory parameters, concomitant medication and study drug exposure)
- Investigate pharmacokinetic/pharmacodynamic relationships in a population pharmacokinetic study in a minimum of 200 patients in the E7389 arm

7. INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan – Description

This is a multi-center, Phase III, open-label, randomized, two-parallel-arm study in breast cancer patients. This study will enroll patients who have had up to three prior chemotherapy regimens, and no more than two prior regimens for advanced and/or metastatic disease. The regimens must have included an anthracycline and a taxane, either in the (neo)adjuvant setting or for locally advanced or metastatic disease. Patients must have documented evidence of progression during or after their most recent anti-cancer therapy.

In addition, patients with known HER2/neu overexpressing tumors (see section 11.1.2) may have been treated with trastuzumab in centers where this treatment is available, and patients with known estrogen and/or progesterone receptor positive disease may have been treated with hormonal therapy. Patients for whom HER2/neu status, estrogen receptor (ER) and progesterone receptor (PR) status are unknown will be accepted into the study.

Patients will be randomized to receive either E7389 as an intravenous (IV) infusion of 1.4 mg/m^2 over 2-5 minutes on Days 1 and 8 every 21 days or capecitabine as an oral administration of 2.5 g/m^2/day administered twice daily in two equal doses on Days 1 to 14 every 21 days. Patients will continue on study until unacceptable toxicity, progression of disease, or until in the opinion of the investigator, discontinuation of therapy is in the best interest of the patient. Patients who demonstrate clinical benefit may continue treatment for as long as clinical benefit is sustained. The study will begin on 01 April 2006, and will end on or before April 2012. The maximum treatment period for each patient on study is anticipated to be 18 weeks, with the exception of those patients who respond to treatment for longer. Patients will be withdrawn if they no longer have clinical benefit, i.e. have disease progression or toxicity.

7.2 Discussion of Study Design, Including the Choice of Control Groups

This is an open-label, randomized, two-parallel arm study comparing E7389 with capecitabine. Patients will be randomized to receive either E7389 or capecitabine on a one to one ratio.

7.3 Definition of End of Study

The end of this study is defined as the final study visit of the last patient to be withdrawn from treatment.

8. SELECTION OF STUDY POPULATION

8.1 NUMBER OF PATIENTS

A maximum of 1100 patients (550 per treatment arm) will be randomized into the trial. To avoid a center effect, any one center may enroll a maximum of 5% of the study population (i.e. 55 patients).

8.2 INCLUSION CRITERIA

1. Female patients with histologically or cytologically confirmed carcinoma of the breast. Every effort should be made to ensure that paraffin embedded tissue or slides from the diagnostic biopsy or surgical specimen are available for confirmation of diagnosis.

2. Patients with locally advanced or metastatic disease who have received up to three prior chemotherapy regimens, and no more than two prior regimens for advanced and/or metastatic disease.*

   - Regimens must have included an anthracycline (e.g. doxorubicin, epirubicin) and a taxane (e.g. paclitaxel, docetaxel), either in combination or in separate regimens
   - Patients must have progressed during or after their last anti-cancer therapy, and this must be documented
   - Patients with known HER2/neu over-expressing tumors (see section 11.1.2) may additionally have been treated with trastuzumab in centers where this treatment is available
   - Patients with known estrogen and/or progesterone receptor-expressing tumors may have additionally been treated with hormonal therapy

   *Any single agent therapy, and any combination of cytotoxic, hormonal, biological targeted agents, and/or humanized antibodies, scheduled to be administered as a pre-planned treatment, given concomitantly, sequentially or both, is considered one regimen. Planned neo-adjuvant chemotherapy (to debulk the tumor prior to surgical intervention) plus postoperative adjuvant chemotherapy is also considered one regimen.
   If, due to toxicity, the dosing of one or more of the components must be reduced, or one or more of the components of the regimen must be omitted, or one of the components must be replaced with another similar drug, the changed version of the original regimen is not considered a new regimen. However, if a new component, dissimilar to any of the original components, is added to the regimen, the new combination is considered a new regimen.
   Prior hormonal therapy, biological therapy (eg, trastuzumab, bevacizumab) or immunotherapy are not to be counted as one of the prior chemotherapy regimens allowed. However, hormonal therapy must be discontinued one week before administration of study treatment, and biological therapy must be discontinued two weeks before study treatment administration.
   If the treatment is interrupted for surgery or radiotherapy, and then continues with an unchanged schedule and components, that treatment is considered as one regimen despite the interruption.

3. Resolution of all chemotherapy or radiation-related toxicities to Grade 1 severity or lower, except for stable sensory neuropathy ≤Grade 2 and alopecia

4. Age ≥ 18 years

5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2 (Appendix 5)

6. Life expectancy of ≥ 3 months

7. Adequate renal function as evidenced by serum creatinine < 1.5 mg/dL or calculated creatinine clearance > 50 mL/minute (min) per the Cockcroft and Gault formula (Appendix 6)

8. Adequate bone marrow function as evidenced by absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, hemoglobin ≥ 10.0 g/dL (a hemoglobin <10.0 g/dL acceptable if it is corrected by growth factor or transfusion), 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, alanine transaminase (ALT), and aspartate transaminase (AST) ≤ 3 x ULN (in the case of liver metastases ≤ 5 x ULN), or in case of bone metastases, liver specific alkaline phosphatase ≤ 3 x ULN

10. Patients willing and able to complete the EORTC quality of life questionnaire (QLQ-C30 with breast cancer module QLQ-BR23) and Pain VAS

11. Patients willing and able to comply with the study protocol for the duration of the study

12. Written informed consent prior to any study-specific screening procedures with the understanding that the patient may withdraw consent at any time without prejudice

8.3 EXCLUSION CRITERIA

1. Patients who have received more than three prior chemotherapy regimens for their disease, including adjuvant therapies, or patients who have received more than two prior chemotherapy regimens for advanced disease (other therapies are allowed e.g. anti-estrogens, trastuzumb and radiotherapy)

2. Patients who have received capecitabine as a prior therapy for their disease

3. Patients who have received chemotherapy, radiation, or biological therapy within two weeks, or hormonal therapy within one week before study treatment start, or any investigational drug within four weeks before study treatment start.
4. Radiation therapy encompassing > 30% of marrow (Appendix 10)
5. Prior treatment with mitomycin C or nitrosourea
6. Pulmonary lymphangitic involvement that results in pulmonary dysfunction requiring active treatment, including the use of oxygen
7. Patients with brain or subdural metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting study treatment. Any symptoms attributed to brain metastases must be stable for at least 4 weeks before starting study treatment; 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 4 weeks earlier.
8. Patients with meningeal carcinomatosis
9. Patients who are receiving anti-coagulant therapy with warfarin or related compounds, other than for line patency, and cannot be changed to heparin-based therapy, are not eligible. If a patient is to continue on mini-dose warfarin, then the prothrombin time (PT) / international normalized ratio (INR) must be closely monitored.
10. Women who are pregnant or breast-feeding; women of childbearing potential with either a positive pregnancy test at screening or no pregnancy test; women of childbearing potential unless (1) surgically sterile or (2) using adequate measures of contraception (considered to be two methods of contraception, one of which must be a barrier method, e.g. condom, diaphragm or cervical cap). Perimenopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.
11. Severe/uncontrolled intercurrent illness/infection
12. Significant cardiovascular impairment (history of congestive heart failure > NYHA grade II, unstable angina or myocardial infarction within the past six months, or serious cardiac arrhythmia) (Appendix 11)
13. Patients with organ allografts requiring immunosuppression
14. Patients with known positive HIV status
15. Patients who have had a prior malignancy, other than carcinoma *in situ* of the cervix, or non-melanoma skin cancer, unless the prior malignancy was diagnosed and definitively treated ≥ 5 years previously with no subsequent evidence of recurrence

16. Patients with neuropathy > Grade 2 at screening
17. Patients with a hypersensitivity to halichondrin B and/or halichondrin B chemical derivative
18. Patients who participated in a prior E7389 clinical trial
19. Patients with other significant disease or disorders that, in the Investigator's opinion, would exclude the patient from the study

8.4 REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients will be discontinued from this study for any of the following reasons:

1. Progressive Disease by clinical evaluation or as documented by RECIST Criteria (Appendix 12)
2. Losing clinical benefit because of undue toxicity
3. The patient withdraws consent
4. The investigator concludes that further therapy is not in the best interest of the patient. In the US this should be done in consultation with the patient's primary physician.

9. TREATMENTS

9.1 IDENTITY OF INVESTIGATIONAL PRODUCT(S): E7389

9.1.1 Drug Substance

Development Code: E7389

Laboratory Code: ER-086526

NIH/NCI No.: NSC-707389

Alternative Name: BOLD

Chemical Name (Chemical Abstract Services):

11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-i]furo[2',3':5,6]pyrano[4,3-b][1,4]dioxacyclopentacosin-5(4*H*)-one, 2-[(2*S*)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*, 12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-, methanesulfonate salt

Chemical Formula: $C_{40}H_{59}NO_{11}\cdot CH_3SO_3H$

Molecular Weight: 826.00

Chemical Structure:

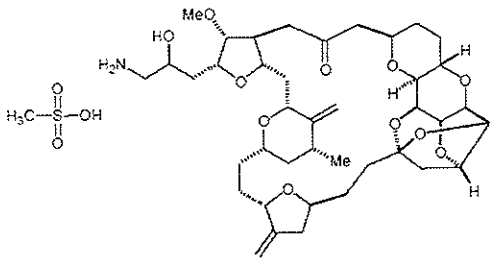

Figure 1: Chemical Structure of E7389

9.1.2 Physical and Chemical Characteristics

Appearance: White powder

Hygroscopicity: E7389 is hygroscopic

Solubility Profile: The solubility of E7389 was determined at room temperature in various organic solvents and water. E7389 was at least freely soluble in *N*-methyl-2-pyrrolidone, methanol, ethanol, acetonitrile, and ethyl acetate; soluble in acetone and 1-octanol; sparingly soluble in water; and very slightly soluble in methyl-*tert*-butylmethyl ether and heptane. E7389 in aqueous buffers (Britton-Robinson buffer, ionic strength = 0.3, pH 2 to pH 11, 25°C) was at least sparingly soluble.

Drug Product: E7389 Eisai Standard 1.0 mg (as mesylate salt) in 0.1 mL ethanol plus 1.9 mL Water for Injection.

9.2 COMPARATOR: CAPECITABINE

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5-deoxy-5-fluorouridine which is converted to 5-fluorouracil (5-FU). Capecitabine is commercially supplied as film-coated tablets for oral administration. Each tablet contains either 150 mg or 500 mg of capecitabine.

9.3 LABELING, PACKAGING AND STORAGE: E7389

Eisai will supply pre-labeled vials containing 1 mg/2 mL E7389 as a 500 µg/mL solution in ethanol/water (5:95).

Clinical supplies for USA, Canadian and South American centers will be manufactured at Catalent, Albuquerque, NM, USA or at Nerviano Medical Science PTS Inc., Viale Pasteur, 10, 20014 Nerviano, Italy. The supplies will be appropriately packaged and labeled for distribution to investigational sites by Aptuit, Inc., Allendale, NJ, USA.

Clinical supplies for European and Rest of World centers will be manufactured at Nerviano Medical Science PTS Inc., Viale Pasteur, 10, 20014 Nerviano, Italy. The supplies will be appropriately packaged and labeled for distribution to investigational sites by Catalent UK Packaging Ltd., Bolton, UK.

Analytical certificates will be retained in the Sponsor's study files.

E7389 will be labeled according to the various national guidelines and translated into local languages as appropriate for the countries participating in the study.

8. Disclosure of financial interests by the Principal Investigator and all sub-investigators listed on FDA Form 1572

9. A signed and dated Curriculum Vitae of the Principal Investigator (PI) including a copy of the PI's current medical license (US) or medical registration number on CV (Europe)

10. A signed Clinical Trial Agreement

The Investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study medication to the study site, the inventory at the site, use for each patient, and destruction of study drug or return of the study drug to a delegate of the Sponsor. The Drug Dispensing Log must be available for monitoring, auditing, or inspection.

9.6 ADMINISTRATION OF TREATMENTS

9.6.1 E7389

Each vial contains 1 mg of E7389 in 2 mL solution (500 µg/ml). Before dose administration, the amount of E7389 needed for each patient must be calculated in the following manner:

1. Scheduled dose (mg/m^2) x body surface area (BSA) (m2) = Dose (mg)
2. Dose (mg) x 2 = the number of mL of E7389 to withdraw from vials for administration

BSA will be calculated using any method that is accepted and customarily used by the clinical site, such as the Mosteller formula:

$$BSA\ (m^2) = ([Height\ (cm) \times Weight\ (kg)]/3600)^{1/2}$$

Height and body weight will be recorded at the Screening visit. Thereafter, body weight will be recorded on Day 1 of each treatment cycle for calculation or adjustment of BSA. The dose will not be adjusted for body weight on Day 8 of the treatment cycles.

The amount of E7389 required (calculated above) will be withdrawn from the appropriate number of vials into a syringe. This may be injected directly as an IV bolus over 2-5 minutes or diluted in up to 100 ml 0.9% sodium chloride (NaCl) for IV infusion over 2-5 minutes.

9.6.1.1 Administration schedule

Therapy will be administered on Days 1 and 8 every 21 days, continuing until reasons for discontinuation specified in section 8.4 are fulfilled. Patients who demonstrate clinical benefit can continue treatment for as long as clinical benefit is sustained. Treatment will be administered on Days 1 and 8 whenever possible. If holidays or personal schedules make

administration on Days 1 or 8 impossible, then administration will be as close to the targeted date as possible. Treatment on Day 1 may be given up to one day earlier or two weeks later. Treatment on Day 8 may be given one day earlier or up to one week later. If Day 8 is delayed beyond Day 15, the second administration in this cycle will be omitted, and treatment will resume as scheduled on Day 1 of the next cycle. Regardless of the time of administration, toxicity from previous treatment must be within acceptable ranges as described below.

9.6.1.2 Dose modification

The dose of E7389 may be reduced or discontinued during any cycle in accordance with the toxicity modifications described in this chapter.

Toxicities will be managed by treatment interruption and dose reduction. Once the dose has been reduced, it cannot be increased at a later date.

9.6.1.3 Treatment in subsequent cycles

Treatment for a subsequent cycle will only occur when ANC on Day 1 is $\geq 1.0 \times 10^9$/L, platelets on Day 1 are $\geq 75 \times 10^9$/L, and all other toxicity of a previous cycle has recovered to $\leq$ Grade 2 (except anemia, alopecia). If treatment has to be rescheduled for any reason, the first day of treatment will be considered Day 1 of the next cycle. If treatment is delayed for more than two weeks, the patient should be withdrawn from the study, unless discussed and agreed with the Sponsor.

9.6.1.4 Dose modification on Day 1

E7389 will be reduced to 1.1 mg/m^2 on Day 1 in case of:

- Hematological grade 3-4 toxicities as described below in the previous cycle, recovered to $\leq$ grade 2:
  1. Grade 4 neutropenia
  2. Grade 3 or 4 neutropenia with fever or infection requiring treatment with growth factors and/or antibiotics
  3. Grade 4 thrombocytopenia
  4. Grade 3 thrombocytopenia requiring platelet and/or blood transfusion
- Non-hematologic grade 3-4 toxicities in the previous cycle, recovered to $\leq$ grade 2 in one week, with or without maximal supportive care

Note: if grade 3-4 hematologic toxicities do not recover to $\leq$ grade 2 in two weeks, or non-hematologic grade 3-4 toxicities to $\leq$ grade 2 in one week, the patient should be removed

from the study; however, if the patient is deemed to have clinical benefit from treatment, continuation of treatment and reduction of the dose must be discussed with the sponsor.

9.6.1.5 Dose modification or reschedule on Day 8

If hematological (ANC < 1.0 x 10^9/L and/or platelet count < 75 x 10^9/L) or non-hematological (any > Grade 2 except inadequately treated nausea and/or vomiting) toxicities occur on Day 8, treatment on that day will be postponed until recovery to these values. The dose will then be reduced to 1.1 mg/m^2. If treatment is rescheduled and can be administered on or before Day 15, the treatment day will be considered the new Day 8. If treatment is delayed beyond Day 15, the second administration in this cycle will be omitted and treatment will resume as scheduled on Day 1 of the next cycle.

9.6.1.6 Subsequent dose modifications

If hematological toxicity, as described in Sections 9.6.1.3 and 9.6.1.4, re-occurs despite dose reduction to 1.1 mg/m^2, and despite the use of growth factors (see section 9.10), the dose should be reduced to 0.7 mg/m^2.

If Grade 3 or 4 non-hematological toxicity re-occurs despite dose reduction to 1.1 mg/m^2, the dose should be reduced to 0.7 mg/m^2.

If grade 3-4 toxicities recur despite the second dose reduction, the patient should be removed from the study.

9.6.2 Capecitabine

Capecitabine will be administered orally at a dose of 2.5 g/m^2/day administered in two equal doses on Days 1 to 14 of each 21-day cycle. The appropriate number of capecitabine tablets (150 mg and 500 mg) to make up a 14-day course will be provided to the patient to be self-administered at home. To ensure global consistency in calculating the starting capecitabine dose, the Capecitabine Dose Calculation tables given in Appendix 4 should be used. Tablets should be taken twice daily with water, at approximately 12-hour (± 30 minutes) intervals, within 30 minutes of the end of a meal.

Full details for capecitabine can be found in the Summary of Product Characteristics, which will be provided separately to sites.

9.6.2.1 Dose modifications

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). Once the dose has been reduced, it should not be increased at a later time. Doses of capecitabine omitted for toxicity are not replaced or restored. Instead the patient should resume the planned treatment cycle.

Table 1: Recommended Dose Modifications with Capecitabine Monotherapy

Toxicity (NCI grade)	During a course of therapy	Dose adjustment for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2[a]		
- 1st appearance[b]	Interrupt until resolved to Grade 0-1	100%
- 2nd appearance[c]	Interrupt until resolved to Grade 0-1	75%
- 3rd appearance[c]	Interrupt until resolved to Grade 0-1	50%
- 4th appearance[c]	Discontinue treatment permanently	
Grade 3		
- 1st appearance	Interrupt until resolved to Grade 0-1	75%
- 2nd appearance[c]	Interrupt until resolved to Grade 0-1	50%
- 3rd appearance[c]	Discontinue treatment permanently	
Grade 4		
- 1st appearance	Discontinue permanently or If investigator deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

[a] Unless pre-existing and unchanged

[b] At the investigator's discretion and if it is in the best interest of the patient the dose of capecitabine may be reduced upon the first instance of Grade 2 toxicity for the following adverse events hand-and-foot syndrome, hyperbilirubinemia, stomatitis, or diarrhea, nausea or vomiting that is not controlled by appropriate supportive medication.

[c] During the same cycle of therapy

9.7 Method of Assigning Patients to Treatment Groups

Randomization to treatment with E7389 or capecitabine will be carried out from a central location through an Interactive Voice Response System (IVRS). Instructions will be provided to sites in a separate document.

9.8 Selection of Doses in the Study

The E7389 dose of 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) was selected from experience in the Phase I and prior Phase II studies. The MTD was determined to be 1.4 mg/m^2 when administered as a bolus on Days 1, 8, and 15 of a 28-day cycle. In two subsequent Phase II studies, in heavily pretreated patients with breast cancer and non-small-cell lung cancer, the Day 15 dose in the 28-day cycle had to be omitted in >50% of cases due to hematologic toxicity. Efficacy, however, was not affected by skipping the Day 15 dose. It was concluded that 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle was likely to be the optimal dose and schedule, and a cohort of patients treated according to this scheme was added to both ongoing studies, to verify its safety.

The dosing and schedule of capecitabine is the dose used in the pivotal study (Ref: FDA Medical Review of NDA 20-896) proving efficacy in second-line treatment of breast cancer.

9.9 BLINDING

This is an open label study.

9.10 PRIOR AND CONCOMITANT THERAPY

All diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded in the CRF including the date, indication, description of the procedure(s) and any clinical findings.

All concomitant treatment, or medication administered during the 30 days preceding first administration of the investigational product and throughout the study until 30 days after the final administration of the investigational product, must be reported on the CRF. The generic name of the drug (or trade name for combination drugs) must be specified along with the total daily dosage, route, duration of treatment, and indication of use.

Any medication considered necessary for the patient's welfare that is not expected to interfere with the evaluation of the study drug may be given at the discretion of the Investigator. Ancillary treatments will be given as medically indicated.

Analgesic medication(s) for tumor pain must also be recorded on the appropriate pages of the CRF during Screening and at each clinic visit to determine if E7389 will demonstrate a clinical benefit regarding pain management.

Any changes in documented, permitted concomitant treatment already being taken at the beginning of the clinical study must be recorded in the space in the CRF reserved for this purpose, noting the type of medication, the dose, duration, and indication.

9.10.1 Concomitant treatments permitted

- Anti-emetics
- Anti-diarrhea therapy
- Anti-allergic measures such as corticosteroids and antihistamines
- Use of granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and erythropoietin is allowed according to ASCO guidelines and local standard practice.
- Patients who are being treated with bisphosphonates when they enter the study may continue the medication as long as the dose is stable. If a change in dose is deemed necessary, the case must be discussed with the Sponsor. If a patient requires initiation of bisphosphonates after starting study treatment, they should be withdrawn from the study.

- Palliative radiotherapy may be given for bone pain or for other reasons (ie, bronchial obstruction, ulcerating skin lesions). The irradiated area should be limited and should not involve more than 10% of the bone marrow. The irradiated area cannot be used for tumor response assessment.

  During palliative radiotherapy, treatment with E7389 should be delayed. Treatment with E7389 may be resumed if the patient has recovered from any radiation-associated toxicity.

- A number of medications are permitted with caution. Drugs that are weak CYP3A4 inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton and clotrimazole. The investigator should monitor patients carefully for potential adverse interaction between these medications and E7389. In case of suspicion of adverse interactions, these medications should be discontinued with careful follow up of the patient until such interaction is resolved. A complete list of drugs that are substrates, inducers or inhibitors of CYP3A4 can be found at http://medicine.iupui.edu/flockhart.

9.10.2 Concomitant treatments not permitted

- Other investigational drugs
- Anti-tumor therapies such as chemotherapy, hormone therapy, radiation therapy (other than required for palliation), gene therapy, biologics, or immunotherapy
- Due to the likelihood of drug interactions with E7389 and warfarin and related compounds, substitution of alternative agents for venous thromboembolic complications or requirement for anticoagulation are mandated. Mini-dose warfarin is permitted. The use of unfractionated heparin (standard, low-dose, or adjusted dose) as well as low molecular weight heparins should be strongly considered for continuation of such patients' participation in this study. If a patient is to continue on mini-dose warfarin or a related compound, then the prothrombin time (PT) / international normalized ratio (INR) must be closely monitored.

10. ASSESSMENTS

10.1 SAFETY

10.1.1 Physical Examination

- Head, eyes, ears, nose, throat (HEENT)
- Neurological
- Respiratory
- Cardiac
- General Abdomen
- Hepatic
- Genital Urinary System
- Musculoskeletal

10.1.2 Vital Signs, Height and Weight

Vital signs at all visits will include temperature, blood pressure, and heart rate

Height and body weight will be measured at the Screening visit. Thereafter, body weight will be recorded on Day 1 of each treatment cycle for calculation or adjustment of BSA. Body weight will also be measured at Study Termination.

10.1.3 Electrocardiograms

12-lead electrocardiograms (ECG) will be taken for all patients at Screening, at the end of Cycle 2, and at Study Termination. ECGs will be complete, standardized 12-lead recordings. Wherever possible, sites should use only ECG machines that display all lead outputs on a single page. In addition to a rhythm strip, a minimum of three full complexes should be recorded from each lead simultaneously. Measurements should be taken with the filter off. Two original print-outs of each ECG will be obtained. One print-out will be collected from the site for a manual read and evaluation by a central reading facility, the other is for the site's own records.

10.1.4 Laboratory Assessments

Local laboratories will perform laboratory tests and the results will be recorded on the CRF. Should tests be performed at a different laboratory, sites should provide details of the laboratory, including normal ranges and certification.

10.1.4.1 Hematology

- Red blood cell count (RBC)
- Hemoglobin (Hb)

- Hematocrit (HCT)
- Platelets
- Total white blood cell count (WBC) with differential
- Absolute Neutrophil Count

10.1.4.2 Clinical Chemistry

- Albumin
- Alkaline Phosphatase
- ALT
- AST
- Bilirubin (total)
- Calcium
- Chloride
- Serum Creatinine
- Glucose (at screening only)
- Lactate Dehydrogenase (LDH)
- Magnesium
- Phosphorous
- Potassium
- Protein (total)
- Sodium

10.1.4.3 Urinalysis

- Dipstick analysis
- Microscopic analysis (if clinically indicated)

10.1.4.4 Pregnancy test

- Serum or urine pregnancy test (if applicable) at Screening and Day 1 Cycle 1 only (may be performed within 72 hours prior to Day 1 Cycle 1)

10.1.5 Data Monitoring Board

A Data Monitoring Board (DMB) will be convened by Eisai (see section 13.7).

10.2 EFFICACY

10.2.1 Tumor Assessments

Baseline tumor assessments, consisting of CT or MRI scans of the chest, abdomen, and pelvis and any other areas of suspected disease, as well as photographs of skin lesions being measured as target lesions, should be performed within 28 days prior to starting study treatment. Tumor marker levels alone are not considered sufficient to assess tumor burden. Chest x-ray alone is not considered sufficient to assess extent of chest disease. The chest, abdomen plus any other areas where disease was found at Baseline will then be scanned/photographed every second cycle (starting Cycle 2) for the first 12 cycles then every third cycle (starting Cycle 15) between Days 15 and 21, or sooner if there is evidence of disease progression. Any new areas of suspected disease identified at these time-points will also be scanned. A radionuclide bone scan using 99m technetium-labeled polyphosphonate scintigraphy should be performed at screening within six weeks prior to start of study treatment and should be repeated every sixth cycle (starting Cycle 6), between Day 15 of the sixth cycle and Day 7 of the following cycle. Tumor response will be confirmed by a second examination (using CT/MRI scans and/or photography, and bone scans) performed no less than four weeks after first observation of response.

If patients discontinue treatment without PD, tumor assessments (except bone scans) should be performed at study termination (within 30 days of last study drug administration) and then every three months until PD or start of another anti-cancer therapy. Radionuclide bone scans for these patients should be performed every six months following study termination until PD or start of another anti-cancer therapy.

In order for the SD designation to be given for best overall response, at least one post-treatment measurement must have met the SD criteria a minimum of five weeks after first study drug administration. CR or PR assessed a minimum of five weeks after start of treatment with a subsequent PD without a confirmation of PR or CR at least four weeks later by follow-up scans but having a subsequent PD assessment will be considered SD for the best response. However, CR or PR assessed less than five weeks of start of treatment with a subsequent PD will be considered PD for the best response.

The preferred type of radiological scan is a diagnostic quality spiral or multi-detector CT scan with IV contrast. If IV contrast is contraindicated, the chest evaluation should be performed with non-contrast CT and abdomen and pelvis evaluation done with MRI. Brain scans, where required, should be performed with IV contrast using either MRI or CT. Ultrasound should not be used for radiological tumor assessment. If a patient has a lesion on chest x-ray at screening or develops a new chest lesion (other than a non-bulky skin lesion), CT (or MRI) scans should be used for tumor response assessment. The same imaging modality and image acquisition protocol (including use of IV contrast or not) should, if possible, be used consistently across all time-points. It is recommended that spiral CT be performed with a 5mm contiguous reconstruction algorithm and that conventional CT and MRI be performed with contiguous slices of 10mm or less in thickness.

If tumor assessment is done by clinical exam (e.g. for skin lesions), the assessment should, if possible, be made by the same investigator throughout the study. If subcutaneous masses or nodes are palpable (i.e. bulky), tumor response assessment should be by radiographic technique (CT/MRI), not clinical exam. If a superficial skin lesion is measurable (≥ 20mm) and cannot be evaluated by CT scan, it should be documented by photography, incorporating a ruler with a millimeter scale in the field of view.

10.2.2 Target and non-target lesions

10.2.2.1 Measurable Disease

According to RECIST criteria[22] (see Appendix 12 for RECIST highlights), measurable disease is defined by the presence of at least one measurable lesion. A measurable lesion is one that can be accurately measured in at least one diameter (at least 10 mm in longest diameter (LD) by spiral computer tomography (CT) scan, or at least 20 mm by standard CT/MRI techniques or by clinical measurement). If a lesion is assessable by both radiological and clinical techniques, radiological techniques should be used. If the only measurable lesion is a lymph node, it must measure at least 20 mm in LD. If a single lesion is identified as the target lesion, a cytological or histological confirmation of breast carcinoma is required.

Target lesions should be selected on the basis of their size (longest diameter) and their suitability for accurate repeated measurements. If palliative radiotherapy is planned for any of the lesions, they should not be selected as target lesions

All measurable lesions up to a maximum of five lesions per organ/site and 10 lesions in total, which are representative of all involved organs/sites should be identified, measured and recorded as target lesions on the appropriate baseline CRF. The same lesions should be measured and recorded at all follow-up time-points.

All other lesions/sites of disease should be identified as non-target disease, recorded on the baseline CRF and assessed at all follow-up time-points (as no change, increased, decreased or absent). Any new lesions detected radiographically should also be recorded on the appropriate CRF. Any new bone lesions identified during the study which are not captured on a CT/MRI scan should be assessed by x-ray to confirm whether or not they are malignant lesions.

10.2.2.2 Clinically Evaluable Disease

Clinically evaluable lesions/sites of disease (such as pleural effusion, ascites, cutaneous lymphangitis) should be identified and recorded as non-target lesions on the appropriate baseline CRF. Measurements of these lesions are not required but they should be followed and recorded as 'no change', 'increased', 'decreased' or 'absent' in the post-treatment CRFs. Additionally, the appearance of any new clinically evaluable lesions should be recorded on

the post-treatment CRFs.

10.2.3 Independent blinded review

For all patients, an independent review will be performed of imaging scans for tumor response. Response will be assessed by RECIST criteria as detailed in an Independent Imaging Review Charter, which will be issued prior to the start of the independent review. Investigators are required to provide copies (preferably in digital format) of images for tumor assessment (CT, MRI, bone scans and x-rays, photographs) to a central facility. A manual detailing recommended scanning parameters, image handling and shipping will be provided to each site.

10.3 CLINICAL BENEFIT ENDPOINTS

10.3.1 Pain intensity

Pain intensity will be measured at Baseline (within seven days of Day 1 Cycle 1) and weekly during the study using a visual analog scale. Patients will be asked to record their pain level weekly at a consistent time of evaluation by marking a single vertical line that crosses a 1-100 mm unmarked visual analogue scale (VAS) (Appendix 9).

10.3.2 Analgesic consumption

Analgesic consumption will be recorded at Baseline and throughout the study.

10.3.3 ECOG performance status

ECOG performance status will be collected at Baseline, Day 1 of every cycle, and at Study Termination.

10.3.4 Quality of Life (EORTC questionnaire)

Quality of Life (QoL) assessments will be performed using the EORTC QLQ-C30 (Appendix 7) questionnaire Version 3.0 with Breast module QLQ-BR23 Version 1.0 (Appendix 8). Assessments will be performed at Baseline (within seven days prior to Day 1 Cycle 1 and before randomization), then at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months after start of treatment. The initial QoL questionnaire must be completed in the clinic before randomization. Post-baseline questionnaires should be completed in the clinic before any study-related procedures are administered or tumor assessment results are communicated to the patient. Questionnaires should continue to be completed at the scheduled time-points (including beyond study termination), until the patient has progressive disease or starts a different course of anti-tumor treatment.

One person in each center must be designated to take responsibility for the administration, collection and checking of the QoL forms. High levels of compliance throughout will be required.

The questionnaires should be completed by the patients without conferring with friends or relatives, and all questions should be answered even if the patient feels them to be irrelevant. Patients should always be asked to complete questionnaires even if they refused on the previous occasion.

Further details about QoL questionnaire administration are provided separately to site staff.

10.4 PHARMACOKINETICS

Pharmacokinetic (PK) samples will be taken for a minimum of 200 patients in the E7389 arm only. Population analysis with sparse sampling collection schedule will be used to characterize the pharmacokinetic profile of E7389. Attempts will be made to identify the covariates that affect drug behavior, or those that explain variability in a heterogeneous patient population. E7389 will be quantified using a validated LC/MS/MS method. Prior to the analysis of study samples, the assay sensitivity, specificity, linearity and reproducibility will be documented. Appropriate nonparametric and/or parametric methods will be used to examine the pharmacokinetic/pharmacodynamic relationships of E7389.

The PK of E7389 will be assessed during the first cycle of treatment only. A total of four samples will be taken from each participating patient, at one time-point from each of the blocks detailed below. The sampling schedule will be assigned at registration. If, for logistical or other reasons, a given sample cannot be taken at the scheduled time-point, it should be taken at the closest possible time and this should be fully documented.

The sampling time points are:

Block 1

- Timepoint T1 Day 1: 5-10 minutes after the start of infusion (ensure infusion has finished before taking sample)

Block 2

- Timepoint T2 Day 1: 15-30 minutes after the start of infusion
- Timepoint T3 Day 1: 30-60 minutes after the start of infusion
- Timepoint T4 Day 1: 60-90 minutes after the start of infusion

Block 3

- Timepoint T5 Day 1: 2-4 hours after the start of infusion
- Timepoint T6 Day 1: 4-8 hours after the start of infusion

Block 4

- Timepoint T7 Day 1: 10-24 hours after the start of infusion
- Timepoint T8 Day 3: 48 hours (±1 hour) after the start of infusion
- Timepoint T9 Day 4: 72 hours (±1 hour) after the start of infusion
- Timepoint T10 Days 5-6: 96-120 hours after the start of infusion

PK kits containing all necessary equipment will be provided. Venous blood will be collected, preferably from the contralateral arm to the infusion, at the time-points according to the sampling schedule the patient is randomized to. If it is not possible to take the blood sample from the contralateral arm, the vein should be flushed after administration and before the PK sample is taken. The arm the infusion is given in and the PK sample taken from will be recorded in the CRF.

At each timepoint, 7 mL of venous blood will be withdrawn into sodium heparinized Vacutainer™ collection tubes. If the patient has a catheter, void volumes to be drawn prior to obtaining the sample will be as specified by the catheter manufacturer.

After collection, blood and anticoagulant should be mixed by gently inverting the tube at least 8-10 times.

Blood samples should be stored on ice and centrifuged within 60 minutes, at 1500g/3000 rpm for 10 minutes at either 4°C or room temperature up to 25°C. Harvest at least 3.5 mL plasma. Plasma will be transferred into two labeled 1.8 mL polypropylene tubes and stored at approximately –70°C until shipment. If a –70°C freezer is not available, samples should be stored at –20°C, but must be shipped within one week.

The tube labels will indicate patient number, site, actual date and time of sample, sampling schedule and time-point. Both tubes for each scheduling time-point should be transported for analysis, but shipped separately, to minimize the risk of accidental destruction of both samples.

Both sets of samples will be shipped as soon as possible after collection, each in a labeled bag with a transmittal form. If possible, the primary and back-up samples should be shipped on separate days. It is important that the information on the tube and bag labels is identical to the information on the transmittal form.

Samples will be shipped on dry ice by Quintiles Laboratories to Eisai Research Institute for batch analysis using a fully validated method. Full sampling and shipment details will be provided in a separate document.

11. SCHEDULE OF ASSESSMENTS

11.1 SCREENING AND ENROLLMENT

11.1.1 Screening

A signed, IRB/IEC-approved, informed consent must be obtained from patients before any study specific procedures or randomization occur.

The following procedures and evaluations must be performed within two weeks prior to start of study treatment:

1. Inclusion/exclusion criteria
2. Baseline tumor assessment (using clinical evaluation or methods of measurement outlined in RECIST criteria [Appendix 12]). Scans for tumor assessment obtained up to 28 days prior to start of study treatment may be used. A radio-isotope bone scan using 99m technetium-labelled polyphosphonate scintigraphy should be performed within 6 weeks prior to start of study treatment.
3. Baseline ECOG Performance Status
4. Demographic data
5. Medical history including prior surgical procedures, treatments, and medications
6. Baseline signs and symptoms
7. Physical examination
8. Vital signs
9. 12-lead ECG
10. Laboratory assessments
11. Serum or urine pregnancy test (if applicable)
12. Height and weight

11.1.2 Randomization

Patients will be pre stratified based on the geographic region and HER-2/neu status (positive, negative or unknown), and then will be randomized to one of the two treatment groups within each stratum in a 1:1 ratio. Randomization will be done in a consecutive sequence within the study. The following procedures will be conducted:

- Once screened, patients who are candidates for randomization will be evaluated for eligibility by the Investigator to ensure that the inclusion/exclusion criteria have been satisfied.

- Patients should be randomized after completion of the baseline EORTC QoL questionnaire (within seven days of Cycle 1 Day 1).
- Randomization will be conducted using an Interactive Voice Response System (IVRS). Sites will be required to enter patient identification and information for stratification. Treatment allocation and a randomization number will be given for each patient.
- Investigators will be notified by Eisai when the study is completed or closed to enrollment, or if the study is placed on administrative hold.

The HER-2/neu status of a tumor may be determined by either immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). The tumor will be considered HER-2/neu positive if the IHC result is 3+ or the FISH test is positive. The tumor will be considered HER-2/neu negative if the IHC results are either 0, 1+, or 2+ or the FISH test is negative. If the results from both tests are available, the FISH test will be considered definitive.

11.2 TREATMENT PERIOD

11.2.1 Day 1 of Each 21-Day Cycle

All pre-dose results should be reviewed by the investigator before study drug administration.

- Serum or urine pregnancy test (if applicable) (Cycle 1 only, may be performed within 72 hours prior to Day 1 Cycle 1)
- ECOG Performance Status
- Pain assessment (VAS), to be performed at baseline within seven days prior to Day 1 Cycle 1
- EORTC Quality of Life assessment at baseline, 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months after start of treatment (prior to tumor assessment) Baseline questionnaires are to be performed within seven days prior to Cycle 1 Day 1
- Physical examination
- AE evaluation
- Concomitant medications and pain medication
- Laboratory assessments including urinalysis (may be performed within 72 hours prior to Day 1 Cycle 1, and within 1 day prior to Day 1 of all other cycles)
- Vital signs
- Weight and BSA (for dose calculation)
- PK sampling (participating patients in the E7389 arm only, Cycle 1 only)

- Infusion of E7389 over 2-5 minutes
  OR
  Oral administration of capecitabine morning and evening

11.2.2 Days 2-7 of Each 21-Day Cycle (capecitabine treatment arm only)

- Oral administration of capecitabine morning and evening

11.2.3 Day 8 of Each 21-Day Cycle

- Pain assessment (VAS)
- Symptom-directed physical examination
- Vital signs
- AE evaluation
- Concomitant medications and pain medication
- Laboratory assessments (not including urinalysis, may be performed within 1 day prior to visit)
- Infusion of E7389 over 2-5 minutes (only E7389 treatment arm)
  OR
  Oral administration of capecitabine morning and evening

11.2.4 Days 9-14 of Each 21-Day Cycle (capecitabine treatment arm only)

- Oral administration of capecitabine morning and evening

11.2.5 Day 15 of Each 21-Day Cycle

To be performed during the first two cycles (and then only as clinically indicated during subsequent cycles):

- Pain assessment (VAS) (to be performed at Day 15 throughout the study, may be performed independently by patient and returned at next visit if no clinic visit is planned on Day 15)
- Symptom-directed physical examination
- Vital signs
- AE evaluation
- Concomitant medications and pain medication
- Laboratory assessments (not including urinalysis, may be performed within 1 day prior to visit)

11.2.6 Days 15-21 every second cycle

- Tumor assessments (except bone scans) are performed every second cycle starting from Cycle 2 between Days 15 and 21 (or sooner if there is evidence of disease progression). The chest, abdomen plus any other areas where disease was found at Baseline will be scanned/photographed. Any new areas of suspected disease identified will also be scanned/photographed. If a patient remains on study for more than 12 cycles, tumor assessment frequency may be reduced to every third cycle.

- ECG (end of cycle 2 only)

11.2.7 Day 15 of every sixth cycle – Day 7 of the following cycle

- Radio-isotope bone scan using 99m technetium-labeled polyphosphonate scintigraphy will be performed every sixth cycle (or sooner if there is evidence of progressive disease) between Day 15 of the sixth cycle and Day 7 of the following cycle.

11.2.8 Study Termination (0-30 days after final dose, or at discontinuation)

- ECOG Performance Status
- Pain assessment (VAS)
- Physical examination
- Weight
- ECG
- Vital signs
- AE evaluation
- Concomitant medications and pain medication
- Laboratory assessments
- Tumor assessment according to RECIST (unless PD has been identified radiographically before termination visit)

11.3 FOLLOW-UP

The investigator must maintain contact every three months, either by telephone or out-patient attendance, with the patient or the patient's family.

Follow-up for patients who terminated the study due to progressive disease will be for survival only and will be performed every three months to document the date and cause of death. Those patients who go off study without PD will be followed for survival and tumor response as well as completion of the QoL questionnaire. Follow-up for both groups will be every three months to document the date and cause of death and for patients without PD, tumor response, while QoL will be according to the frequency described in Section 10.3.4. Tumor assessment data collection and QoL questionnaire completion will be discontinued upon progression of the tumor and/or if the patient goes onto other anti-cancer treatment.

12. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND REPORTING

12.1 ADVERSE EVENTS, SEVERITY AND RELATIONSHIP

Adverse Event (AE): Any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An adverse event does not necessarily have a causal relationship with the medicinal product. For this study the medicinal products are E7389 and capecitabine.

- All adverse events encountered during the clinical study will be reported on the Case Report Form. All adverse events, regardless of relationship to study drug or procedures, should be collected beginning from the time the subject signs the study consent. Adverse Events in clinical investigation subjects include any change from the subject's condition. This includes symptoms, physical findings or clinical syndromes.

- An abnormal laboratory value may be considered an adverse event if the identified laboratory abnormality leads to any type of intervention whether prescribed in the protocol or not. It is up to the investigator to determine whether an abnormal laboratory value constitutes an adverse event.

- Examples of laboratory abnormalities which should be considered as adverse events include those which result in withdrawal of the study treatment, withholding study treatment pending some investigational outcome, reduction of dose of the study treatment or additional concomitant treatment. All laboratory abnormalities considered to constitute an adverse event should be reported on the appropriate page of the Case Report Form (CRF). Laboratory abnormalities do not need to be listed as separate adverse events if they are considered to be part of a clinical syndrome that is being reported as an adverse event.

- It is the responsibility of the investigator to review all laboratory findings in all subjects. Abnormal values should be commented upon as to clinical relevance or importance on the CRF or the laboratory report as appropriate. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

Every effort must be made by the investigator to categorize each adverse event according to its severity and its relationship to the study treatment.

12.1.1 Assessing Severity of Adverse Events

Adverse events will be graded on the five-point scale according to the NCI Common Terminology Criteria (CTC) version 3. Where a CTC grade does not exist for the adverse event, the event will be graded on a three point scale (mild, moderate, severe) and reported in the detail indicated on the Case Report Form. The definitions are as follows:

MILD	Discomfort noticed, but no disruption of normal daily activity.
MODERATE	Discomfort sufficient to reduce or affect normal daily activity.
SEVERE	Incapacitating, with inability to work or to perform normal daily activity.

12.1.2 Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an adverse event to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment.
- The course of the event, considering especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable.
- Whether the event is known to be associated with the study treatment, or with other similar treatments.
- The presence of risk factors in the study subject known to increase the occurrence of the event.
- The presence of non-study treatment related factors which are known to be associated with the occurrence of the event.

12.1.3 Classification of Causality

Not Related: A causal relationship between the study treatment and the adverse event is not a reasonable possibility.

Related: A causal relationship between the study treatment and the adverse event is a reasonable possibility. The investigator must further qualify the degree of certainty as "**possible**" or "**probable**."

12.2 SERIOUS ADVERSE EVENTS

12.2.1 Definition of Serious Adverse Events

A serious adverse event (experience) or reaction is any untoward medical occurrence which:

- Results in death
- Is life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

The following hospitalizations are not considered to be Serious Adverse Events because there is no "adverse event" (i.e. there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug

12.2.2 Reporting of Serious Adverse Events

All Serious Adverse Events, irrespective of relationship to study treatment, must be reported as soon as possible but no later than one business day. The "Clinical Trial Serious Adverse Event Report Form" (SAE form) must be completed and sent to PRA Safety and Risk Management (SRM) by fax at the following numbers:

North America, South America, Australia, New Zealand:

Toll-free fax number for the sites to fax SAE reports to SRM:
+1-877-276-3444
(alternate: +1-913-307-5750)

To speak with a North American Drug Safety associate call 800-772-2215 (US/Canada) or +1-434-951-3489 (South America/Australia/New Zealand) and ask for Drug Safety.

For urgent SAE-related medical issues, please contact the PRA Medical Director:
Tel: +44 1792 525608
Fax: +49-621-87-82-181 (Safety unit in Mannheim, Germany)
E-mail: OncoEU@PRAIntl.com

Europe, Africa, Rest of World:

Fax number for the sites to fax SAE reports to SRM:
+49-621-8782-181
To speak with an EU Drug Safety associate call +49-621-87-82-154.
For urgent SAE-related medical issues, please contact the PRA Medical Director:
Tel: +44 1792 525608
Fax: +49-621-87-82-181 (Safety unit in Mannheim, Germany)
E-mail: OncoEU@PRAIntl.com

Deaths and life-threatening events should be reported immediately by fax to PRA at the following number:

Fax: +49-621-8782-181 (in Europe)

The immediate report should be followed up within one business day by faxing a completed SAE form to the appropriate regional PRA fax number (see above).

It is very important that the serious adverse event report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality. Any follow-up information received on serious adverse events should be forwarded to PRA within one business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Serious adverse events, regardless of causality assessment, must be collected through the termination visit and for **30 days** following study drug discontinuation, whichever is longer.

Any serious adverse event judged by the investigator to be related to the study treatment should be reported to the Sponsor regardless of the length of time that has passed since study completion.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports and other documents requested by the Sponsor.

For urgent safety issues call:

Eisai Inc,
Drug Safety: Eisai Medical Services
Physician On-call
Tel: +1-888-274-2378 (in the USA)

Pharmacovigilance Department,
Eisai Ltd
Global Safety Officer for Eribulin
Tel: +44-208-600-1400 extension 1271

The investigator should notify the Institutional / Ethics Committee of the occurrence of the serious adverse event, in writing, in accordance with local requirements. A copy of this communication must be forwarded to PRA.

12.3 Pregnancy Reporting

Any pregnancy where the estimated date of conception occurred either prior to the study termination visit or within 30 days of the last study treatment must be reported. If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment. An induced abortion or spontaneous abortion is considered to be a serious adverse event and

should be reported in the same timeframe and in the same format as all other serious adverse events.

Pregnancies must be reported as soon as possible, but no later than one business day after the investigator becomes aware of it, by fax to the same contact and number as detailed in Section 12.2.2 for Serious Adverse Event reporting.

The "Pregnancy Report Form" must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but not later than one business day after the investigator becomes aware of it. The "Pregnancy Outcome Form" must be used for reporting the outcome of the pregnancy.

A subject who becomes pregnant must be withdrawn from the study.

13. STATISTICAL METHODS

13.1 DETERMINATION OF SAMPLE SIZE

A total of 1100 patients (550 patients per group) will be enrolled into this trial, randomized to treatment with either E7389 or capecitabine. To avoid a center effect, any one center may enroll a maximum of 5% of the study population (i.e. 55 patients).

Justification of the Total Sample Size:

The sample size calculation is based on a superiority test for comparing overall survival between the two groups treated with E7389 or capecitabine. When the total number of events (deaths) observed is 905, an overall 0.04 level two-sided log rank test has approximately 90% power to detect a difference between the two survival curves if the alternative hypothesis hazard ratio is 0.80 (a 3-month increase in median survival over the 12-month median survival of capecitabine). To account for censoring, the study will enroll 1100 patients. This will correspond to 50 patients per month (22 months of accrual) and total study duration of 45.7 months. These calculations take two interim analyses into account (one at 453 deaths, and a second at 603 deaths). Standard software, East 4.0 was used to calculate the number of required events in this study.

13.2 STATISTICAL PLAN

Unless otherwise mentioned, all tests will be two-sided.

13.2.1 Primary Efficacy Endpoints

13.2.1.1 Overall Survival (OS)

OS is measured from the date of randomization until date of death from any cause or the last date the patient was known to be alive.

13.2.1.2 Progression-Free Survival (PFS)

PFS is measured from the date of randomization to the date of recorded progression of the disease or the death of the patient from any cause. Censoring rules are specified in Table 2. Tumor response data utilized in the main analysis of PFS will be obtained from an independent review of the imaging scans.

13.2.2 Secondary Endpoints

- Quality of Life measured using the EORTC questionnaire
- Objective tumor response rate as measured using RECIST criteria
- Duration of Response
- One, two and three year survival
- Tumor Related Symptom Assessments measured by pain intensity (VAS), and analgesic consumption.

- Safety parameters (adverse events, laboratory parameters, concomitant medication, and study drug exposure)
- Population pharmacokinetics in the E7389 arm

13.2.3 Definition of study populations for analysis

Intent-To-Treat (ITT) Population: The Intent-to-Treat Population consists of all patients who are randomized. This will be the primary analysis population for the efficacy data.

Per-Protocol Population: The Per-Protocol Population consists of patients who are ITT, fulfill all inclusion and exclusion criteria and are treated according to protocol for at least one full cycle. This analysis population will be used for exploratory purposes.

Safety Population: All patients who have received at least one dose of study treatment.

13.3 Analysis of Baseline and Demographic Variables

The demographics and Baseline characteristics including disease history and prior therapy will be summarized using descriptive statistics.

13.4 Efficacy Analyses

Tumor response data utilized in the main analysis of PFS, ORR and duration of response will be obtained from an independent review of the imaging scans. In addition, these analyses will be performed using the investigators' determination of tumor response, which will be considered secondary. Detailed methodology for assessment by independent review will be provided in an Independent Imaging Review Charter.

13.4.1 Decision Rules and Adjustment of Alpha for Primary Endpoints

The study will be declared positive if any of the following outcomes are achieved:

1. First interim analysis after 453 deaths: Overall survival of E7389 is statistically significantly better compared to capecitabine ($p \leq 0.002$),

2. Second interim analysis after 603 deaths: Overall survival of E7389 is statistically significantly better compared to capecitabine ($p \leq 0.0081$),

3. Final analysis after 905 deaths: Overall survival of E7389 is statistically significantly better compared to capecitabine ($p \leq 0.0372$),

4. Final analysis after 905 deaths: Overall survival hazard ratio (E7389/capecitabine) is < 1 ***and*** progression free survival of E7389 is statistically significantly better compared to capecitabine ($p \leq 0.01$).

Decisions will be based on two-sided stratified log-rank tests with HER2/neu status and geographic region as strata.

The overall significance level alpha of 0.05 will be adjusted for the multiple endpoints: 0.04 will be used for testing overall survival, and 0.01 will be used for testing progression free survival.

The trial can be stopped early for superiority on overall survival, but not on progression free survival. To maintain an overall level of 0.04, alpha spending for sequential analyses of overall survival will be based on the Lan-DeMets implementation of the O'Brien-Fleming spending function. With this approach, the nominal significance level of the first interim test will be 0.002, the nominal level of the second will be 0.0081, and the nominal level of the final analysis will be 0.0372.

13.4.2 Analysis of Primary Efficacy Endpoints

13.4.2.1 Overall Survival

Overall Survival (OS), is measured from the date of randomization until date of death from any cause. Patients who are lost to follow-up and the patients who are alive at the date of data cut-off will be censored at the date the patient was last known alive.

Final Analysis: Overall survival will be compared between the two groups using a two-sided, stratified log-rank at a nominal level of 0, 0.0372.
Hypothesis to be tested are:

$H_0: S_{E7389} = S_{Capecitabine}$
$H_a: S_{E7389} \neq S_{Capecitabine}$
Where S is the survival distribution of overall survival.

The p-value from the two-sided, stratified log-rank test will be presented. The stratification factors will be HER2/neu status and geographic region.

In subsequent analyses, treatment effect estimates will be summarized using 95% confidence intervals. Median and 95% CI will be provided for each treatment group. Kaplan-Meier plots will be provided for overall survival. Hazard ratio (E7389/Capecitabine) will be computed together with the 2-sided 95% CI using stratified Cox regression model with treatment as a factor and HER2/neu status and geographic region as strata in the model for the ITT population.

One-, two-, and three- year survival will be estimated from the Kaplan-Meier curve. Comparisons between the two groups will be tested at each time. Additional exploratory Cox regression analysis will be performed for adjusting for covariates age group (≤ 65, > 65 years), HER2/neu status (positive, negative or unknown), ER and PR status (positive, negative or unknown), geographic region, number of prior chemotherapy regimens given for

advanced or metastatic disease (0, 1, 2), and time to progression after the last chemotherapy (≤ 6 months, > 6 months). Also, additional covariates include the setting of prior chemotherapy (anthracyclines and taxanes both received as adjuvant therapy versus at least one of them received as treatment for metastatic disease), and whether patient progressed while on treatment with a taxane or other tubulin-active agent.

Analysis will be performed on the ITT, and per-protocol populations. ITT population will be considered the primary population for the analysis.

13.4.2.2 Progression Free Survival

Analysis will be performed on the ITT, and per-protocol populations. Hence, the main analysis of PFS will be based on the ITT population using the independently reviewed tumor response data.

Progression-Free Survival (PFS) is measured from the date of randomization to the date of documented progression of the disease or death from any cause. Table 2 defines the censoring rules for PFS, and will be considered the primary approach to censoring.

PFS will be compared between the two treatment groups using a two-sided 0.01 level stratified log-rank test. Hazard ratio (E7389/capecitabine) will be provided together with the two-sided 95% confidence interval using stratified Cox regression model with treatment as a factor and HER2/neu status and geographic region as strata. Median and 95% CI will be provided for each treatment group. PFS will be summarized using Kaplan-Meier plots. Six- and twelve-month PFS rates will be provided together with 95% CI. Comparisons between the two groups will be tested at each time.

Additional exploratory Cox regression analysis will be performed for adjusting for covariates age group (≤ 65, > 65 years), HER2/neu status (positive, negative or unknown), ER and PR status (positive, negative or unknown), geographic region, number of prior chemotherapy regimens given for advanced or metastatic disease (0, 1, 2), and time to progression after the last chemotherapy (≤ 6 months, > 6 months). Also, additional covariates include the setting of prior chemotherapy (anthracyclines and taxanes both received as adjuvant therapy versus at least one of them received as treatment for metastatic disease), and whether patient progressed while on treatment with a taxane or other tubulin-active agent.

In addition to the censoring rules specified in Table 2, sensitivity analyses will be performed on the PFS using different approaches to censoring. Details will be specified in a separate statistical analysis plan.

Table 2: Censoring Rules for Progression Free Survival

Situation	End Date	Censored
Documented PD during the study	Date of the first assessment of the series of the tests that determined PD	No
Death during the study before PD	Date of death	No
Treatment discontinuation for other than PD or death, and no post baseline tumor assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death with post-baseline tumor assessments	Date of last tumor assessment	Yes
New anticancer treatment started	Date of last tumor assessment before start of new treatment	Yes
Patients still on treatment without PD as of data cut-off	Date of last tumor assessment	Yes
Discontinued due to PD but no independent review session (clinical progression between scheduled assessments)	Date of last tumor assessment before discontinuation	Yes
Death or PD after two or more missed tumor assessments	Date of last tumor assessment before missed assessments	Yes
Unreadable baseline assessment but readable post-baseline assessments	Date of randomization	Yes

In addition to the censoring rules provided in Table 2, the Independent Review Charter will describe the rules for handling missing time points and imputation of the Date of Progression when there are missing or unreadable assessments.

13.4.3 Analysis of Secondary Efficacy Endpoints

Secondary efficacy endpoints include objective tumor response rate as measured by RECIST criteria and duration of response. Analysis will be performed on both the ITT and the per-protocol populations utilizing response data obtained from the independent review of the imaging scans as well as investigators' determination. Hence, the main analysis of ORR and Duration of Response will be based on the ITT population using the independently reviewed tumor response data.

Objective Response Rate (ORR) is defined as the number of patients with complete response or partial response divided by the number of patients in the analysis population. Response rate will be compared between the two groups using a Fisher's exact test. Response rate will be summarized together with the 95% CI for both groups.

Duration of Response is defined as the time from first documented CR or PR until disease progression or death from any cause. It is measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented. In case of the patient first reaching PR and later CR, the duration of CR will be measured and reported separately, starting from the date when first documented, and ending when a progressive disease is diagnosed, or the patient dies.

For duration of response, Kaplan-Meier plots will be provided. Median and the 95% confidence interval will be provided.

13.5 Analysis Of Clinical Benefits Endpoints

13.5.1 Quality of Life (QoL)

Quality of Life (QoL) will be assessed using the EORTC quality of life questionnaire. The questionnaire consists of a core questionnaire (QLQ-C30) and a tumor site-specific module (e.g., QLQ-BR23 for breast cancer). The QLQ-C30 is composed of both multi-item and single scales. Initially, single scores and multiple-point scales and change from baseline will be summarized at each measurement occasion through graphic displays, summary statistics and percent frequencies of response by treatment arm. The primary QoL analysis will focus on the scores for questions 29 (How would you rate your overall health during the past week?) and 30 (How would you rate your overall quality of life during the past week?) of the global quality of life questionnaire at week 6. The difference in QoL scores at week six between the treatment arms will be compared using a Wilcoxon Rank-Sum test separately for the two questions. Overall significance level of 0.05 will be distributed equally for analyzing these two questions. Hence, the testing will be performed at a 0.025 level.

In addition, to account for longitudinal and missing data, appropriate analyses will be performed including pattern-mixture models[23, 24] which divide the sample into strata defined by length of survival and estimate a separate longitudinal model for the QoL outcome within each pattern. The mean outcomes by survival pattern will be plotted. Using these data, best longitudinal models will be identified for all strata/treatment group combinations simultaneously, with perhaps different parameters within each stratum/treatment group. For example, if a linear trend in time is best, a separate intercept and time slope will be identified within each stratum. SAS Proc Mixed will be used in estimating pattern mixture models[24]. To test for differences between treatment arms, best-fitting models will be estimated and tested for effects of treatment on QoL profile within strata, then combine the tests across strata.

Similar comparisons will be performed on the multi-item and single item subscales. These analyses will be considered exploratory.

Imputation of the missing values, will be performed according to the methods described in EORTC Scoring Manual and P. M. Fayers et al and D.L. Fairclough[25,26]. These methods will be described in a separate statistical analysis plan.

13.5.2 Tumor-Related Symptom Assessments

Exploratory analysis of tumor-related symptom assessments will be performed on both the ITT and the per-protocol populations.

Tumor-related Symptom assessments will be based on change from baseline in pain intensity and analgesic use. Observed values and change from baseline will be summarized at each measurement occasion through summary statistics. Mean values and change from baseline over time will be presented graphically. For the pain intensity (VAS) and analgesic use, pattern-mixture models[23, 24] will be used based on linear mixed models[24], as described above for the EORTC-QLQ outcome scales.

Another objective of this analysis is to estimate the proportion of patients who demonstrate improvement in tumor-related symptoms that were present at baseline. Patients will be classified as symptomatic at screening if they have a visual pain analog score of ≥20 mm on a 100-mm scale, or consumption of any narcotic analgesics in the past week. At the time of each tumor assessment, patients will be classified as improved, no change or worsened since baseline on the three components separately if criteria are met (Table 3) for at least two consecutive assessments.

Table 3: Classifications for Post-Baseline Tumor-Related Symptom Assessments

	Pain Intensity	Analgesic Use
Improved	Decreased ≥ 50%	Decreased ≥ 50%
No Change	Increase/decrease <50%	Increase/decrease <50%
Worsened	Increased ≥ 50%	Increased ≥ 50%

The number and percent of patients who were improved, not changed or worsened will be presented for each of the three assessments. A patient will be considered a clinical benefit responder if they are classified as "improved" in both categories: pain intensity and analgesic use combined. Responders in the two groups will be compared using a chi-square test.

13.6 Safety Analysis

Safety analyses will be performed on the safety population. All safety summaries will be provided according to the actual treatment that the patients received.

13.6.1 Adverse Events

Adverse Events will be regarded as treatment emergent adverse events if they started on or after the date and time of administration of the first dose of study drug, or if they were present prior to the administration of the first dose of study drug and increased in severity during the study.

Overall patient safety will be evaluated by tabulating reports of treatment emergent adverse events. AEs will be summarized using number and percent in the following sets of tables: all events: all events by CTC grades, AEs of interest; and all events by relationship to study drug.

13.6.2 Deaths, Other Serious and Other Significant Adverse Events

Patients who died during the study will be listed. Patients with serious adverse events will be listed. Discontinuations due to AEs will be summarized using number and percent by individual event.

13.6.3 Clinical Laboratory Parameters

For each laboratory value and change from baseline, summaries will be made via descriptive statistics mean, median, standard deviation, and range. A summary table showing incidence of clinically significant Treatment Emergent Abnormal Laboratory Values (TEAVs) and CTC grades will be displayed.

13.6.4 Other Safety Parameters

Other safety parameters such as vital signs, physical exam findings, concomitant medications, and drug exposure will be summarized using descriptive statistics by treatment group.

13.6.5 Analysis of Pharmacokinetic Variables

Appropriate nonparametric and/or parametric methods will be used to examine the pharmacokinetic/pharmacodynamic relationships of E7389.

13.7 INTERIM ANALYSES AND SAFETY: DATA MONITORING BOARD (DMB)

An independent Data Monitoring Board (DMB) will review the safety data periodically, summarizing this at the end of the study for both treatment groups, and the efficacy data from the interim analyses. The DMB will provide recommendations whether to stop or continue the trial based on their efficacy and safety findings. The statutes of the DMB will be defined in advance and will be included in a separate charter. To avoid possible bias, unless the decision is made to terminate the trial, the DMB will not disclose any other results than the recommendation to continue.

Two interim analyses will be performed, one after 50% of the total deaths (453 deaths) have been observed, and a second analysis after 67% of the total deaths (603 deaths) have been observed. The first interim analysis will be performed at a two-sided alpha level of 0.002, the

second will be performed at the nominal 0.0081 level. If the two-sided log-rank test for comparing overall survival is significantly better for E7389 at above mentioned nominal alpha levels at each of the interim analyses, the trial will be stopped for superiority. The trial may also stop for inferiority if E7389 is significantly worse than capecitabine. The trial will not be stopped early due to positive results for progression free survival.