22 May 2014
EMA/441074/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Halaven

International non-proprietary name: ERIBULIN

Procedure No.: EMEA/H/C/002084/II/0011

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

BOR	best overall response
BR23	EORTC breast cancer-specific quality of life questionnaire
CAP	capecitabine
CAPE	capecitabine
CBR	clinical benefit rate
CI	confidence interval
CNS	central nervous system
CR	complete response
CSR	clinical study report
DOR	duration of response
E7389	eribulin
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research on the Treatment of Cancer
ER	estrogen receptor
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
HalB	halichrondrin B
HER2	human epidermal growth factor receptor 2
HER2/neu	human epidermal growth factor receptor 2
HR	hazard ratio
IHC	immunohistochemical
IRC	Independent Radiographic Review Charter
ITT	intent-to-treat
i.v.	intravenous(ly)
IVRS	Interactive Voice Response System

nMFS	new metastasis-free survival
ORR	objective response rate
OS	overall survival
PD	progressive disease OR pharmacodynamic(s), depending on context of use
PFS	progression-free survival
PP	per protocol
PR	partial response OR progesterone receptor, depending on context of use
PS	performance status
QLQ-C30	Quality of Life Questionnaire-Core 30
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	stable disease OR standard deviation, depending on context of use
US	United States
VAS	visual analog scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eisai Europe Ltd. submitted to the European Medicines Agency on 4 April 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Halaven	ERIBULIN	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. Consequently, the MAH proposed the update of sections 4.5, 4.8, 5.1 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Dr Filip Josephson Co-Rapporteur: Dr Jens Ersbøll

Submission date:	4 April 2013
Start of procedure:	26 April 2013
Rapporteur's preliminary assessment report circulated on:	19 June 2013

Rapporteur's updated assessment report circulated on:	19 July 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 July 2013
MAH's responses submitted to the CHMP on:	18 October 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	29 November 2013
Rapporteur's final assessment report on the MAH's responses circulated on:	13 December 2013
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	19 December 2013
MAH's responses submitted to the CHMP on:	17 February 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	5 March 2014
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	20 March 2014
MAH's responses submitted to the CHMP on:	16 April 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	29 April 2014
Rapporteur's updated assessment report on the MAH's responses circulated on:	16 May 2014
CHMP opinion:	22 May 2014

2. Scientific discussion

2.1. Introduction

Halaven (eribulin mesilate) is a non-taxane, microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. It is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease, and administered intravenously on days 1 and 8 every 21 days.

The scope of this type II variation is to extend the indication from the current 3rd line treatment to 2nd line treatment of advanced/metastatic breast cancer.

The proposed indication is based on a subset of the population of the pivotal Study 301, which was a 1:1 randomised open-label study comparing the efficacy and safety of eribulin and capecitabine monotherapy in the first - third line setting. Fifty percent of the eribulin-treated patients in Study 301 were treated in the 2nd line, which represents the new indication sought. 15% of patients were HER2 positive; concomitant HER2-targeted therapy was not allowed during study.

2.2. Non-clinical aspects

2.2.1. Pharmacology

Primary pharmacodynamic studies

The studies included in the current application were specifically selected for presentation because they provide plausible mechanistic explanations for the clinical finding that eribulin has greater effects on overall survival compared to progression-free survival endpoints in metastatic breast cancer. These nonclinical pharmacology studies support the concept that eribulin has additional, previously unrecognized antitumor mechanisms of action that go beyond its previously established direct cytotoxic effects on tumour cells due to its known antimitotic activities.

In vitro and in vivo pharmacodynamic studies were conducted in order to examine effects of eribulin mesilate on: a) tumour vascular function and vascular remodelling, b) migration and invasiveness capacity of cancer cells, and c) epithelial-mesenchymal transition (EMT)-related pathways in both cancer cells and their host tissue counterparts within the tumour microenvironment. The results of these studies are summarised in the following table:

Table 1. Non-clinical primary pharmacology eribulin studies

Tumor Biology Endpoints	Key Effects of Eribulin Mesilate	Study Nos.
Tumor vascular function and remodeling	• Inhibited HUVEC and HBVP proliferation at similar concentrations to those causing antiproliferative effects in MX-1 and MDA-MB-231 human breast cancer cell lines • Potently affected endothelial cell-pericyte vascular networks (i.e., shortening of pre-formed networks) in vitro, in contrast to paclitaxel, 5-FU, and doxifluridine • Significantly changed expression levels of genes related to angiogenesis in pre-formed vascular networks in vitro, whereas 5-FU and doxifluridine did not • Improved vascular function of breast cancer tumors, whereas capecitabine did not, as assessed by: – real-time DCE-MRI-based measurements of vascular perfusion and permeability (K^{trans}) in tumor cores – iAUC measurements showing equalization of vessel architecture across the tumor rim and core – tumor vascular perfusion of Hoechst 33342 dye • Increased both tumor microvessel density and the proportion of smaller microvessels, while simultaneously decreasing the proportion of larger microvessels in MX-1 and MDA-MB-231 human breast cancer xenografts • Significantly altered the expression of angiogenesis pathway genes in host (mouse) tissues and increased murine VEGF protein within the microenvironments of MX-1 and MDA-MB-231 human breast cancer xenografts	BIOMA-2012-124 M12015 M12041 M12016 BIOMA-2012-096 BIOMA-2012-131 120124 M12040 W-20130045[a] M12042 M12043 M12044 M12046 M12053
Metastatic and invasiveness capacity	• Directly reduced the migration and invasiveness potential of MX-1 human breast cancer cells in vitro whereas 5-FU had minimal effects on these processes	M12050
EMT/MET balance	• Induced a phenotypic shift from a mesenchymal to an epithelial phenotype (based on morphology, gene expression, and protein expression) in MX-1 human breast cancer cells in vitro whereas 5-FU had a much weaker effect • Upregulated epithelial marker genes and proteins (e.g., E-cadherin) in MX-1 human breast cancer xenografts • Downregulated mesenchymal marker genes and proteins (e.g., N-cadherin, vimentin, ZEB1) in MX-1 human breast cancer xenografts • Significantly altered the expression of EMT-related pathway genes in host (mouse) tissues within the microenvironments of MX-1 and MDA-MB-231 human breast cancer xenografts	M12055 M12056 M12044 M12052 BIOMA-2012-128

5-FU = 5-fluorouracil, DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging, EMT = epithelial-mesenchymal transition, HBVP = human brain vascular pericytes, HUVEC = human umbilical vein endothelial cells, iAUC = initial area under the curve, K^{trans} = volume transfer constant between blood plasma and extracellular space, MET = mesenchymal-epithelial transition, VEGF = vascular endothelial growth factor, ZEB1 = zinc finger E box binding homeobox 1.

a: Report No. instead of Study No.

The MAH propose that these new data point to an interesting new biology associated with eribulin mesilate treatment that goes well beyond aspects that might be expected simply on the basis of classical antimitotic, antiproliferative effects against cancer cells. The studies point to significant effects of eribulin mesilate on tumour cell biology and tumour host interactions that could provide a plausible and scientific basis for an increase in overall survival despite continued presence, or even growth, of tumours and metastasis. Thus, these findings suggest that eribulin mesilate, in addition to having primary anticancer effects associated with classical cytotoxicity, also renders residual tumours less aggressive and less likely to metastasize. These results support the concept that after eribulin mesilate treatment, residual tumours become less life-threatening and "easier to live with" in contrast to the effects of fluoropyrimidines (e.g., capecitabine), and provide a reasonable mechanistic explanation for the trend towards increased overall survival in eribulin-mesilate–treated subjects with metastatic breast cancer when compared to capecitabine treatment, even in the absence of an increase in progression-free survival.

2.2.2. Ecotoxicity/environmental risk assessment

New environmental risk assessment has been performed in support of the new proposed indication. The Applicant has experimentally established log K_{ow} to 2.25. This is below the threshold of 4.5 and an assessment for persistence, bioaccumulation and toxicity (PBT) is not required.

Table 2: Summary of main study results

Substance (INN/Invented Name): Eribulin mesilate (HALAVEN 0.44 mg/mL)					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	Study No D06022 Shake flask method	2.25			Potential PBT (N)
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined (e.g. prevalence, literature)	0.000066	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Ready Biodegradability Test	OECD 301B	ThCO$_2$: 2.18 CO$_2$/mg Relative degradation 28 days: 7-8%			(modified Sturm)
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Acute static toxicity study in *Daphnia magna*	OECD 202	NOEC	0.46	mg/L	24h EC_{50}: 6.9 mg/L 48h EC_{50}: 0.79 mg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	56	mg/L	

2.2.3. Discussion on non-clinical aspects

An attempt is made to address the pharmacology of eribulin in order to get further understanding on the clinical picture. The ideal situation is to generate such data in advance and use these data to define the most optimal clinical use of the product. It may however also be possible to use nonclinical data to support clinical data in cases like this one, where the clinical picture is unclear and the outcome of different endpoints are not fully consistent. For this purpose it is however of importance to generate data which may help in translating in vitro and/or animal data into the clinical situation. Such translation could include relevant pharmacodynamic biomarkers identified in the animal studies and then studied in clinical material. Such data are considered essential given the fact that animal xenograft studies are known not to share all aspects of the clinical therapeutic situation.

The presented data are interesting and indicate a plausible biological mechanism for some part of the difference between overall survival and progression-free survival observed in Study 301 which could be of clinical importance. However, the interpretation of data is complicated by the fact that in several of the situations where eribulin treatment has been compared to other agents, there is a pronounced difference in anti-tumour activity with eribulin being clearly superior. This means that the quantitative and/or qualitative differences seen on the studied biological markers could be just a consequence of the difference in anti-tumour activity.

In the ERA submitted, the Applicant has experimentally established log K_{ow} to 2.25. This is below the threshold of 4.5 and an assessment for persistence, bioaccumulation and toxicity (PBT) is not required.

2.2.4. Conclusion on the non-clinical aspects

While the non-clinical data are interesting, they do not allow extrapolation to the clinical situation. However, they indicate a plausible biological mechanism for some part of the difference between overall survival and progression-free survival observed in Study 301.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Clinical pharmacology

Included in the current submission is an updated Population Pharmacokinetic (PPK) Analysis, based on pharmacokinetic (PK) data from previous studies as well as from the new Phase 3 Study 301 and a new PK/PD analysis of the relationship between eribulin plasma exposure and different efficacy or safety measures, based on data from Study 301 only. The MAH does not suggest any changes to the SmPC or other claims based on this analysis. In addition, in response to the CHMP request, the MAH performed a physiologically-based pharmacokinetic modelling (PBPK) and simulation exercise to predict the effect of eribulin on a sensitive CYP3A4 substrate.

2.3.2.1. Population pharmacokinetic model

A PPK analysis was previously conducted based on data from seven Phase 1 studies (E7389-A001-101, E7389-A001-102, E7389-E044-103, E7389-J081-105, E7389-E044-108, E7389-E044-109, and E7389-E044-110) and one Phase 2 study (E7389-G000-211). This analysis was discussed during the original MAA for Halaven. The analysis has now been updated to include also data from the new Phase 3 study (E7389-G000-301).

The objectives of the population PK analysis were to describe the PK profile of eribulin in subjects with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes and to identify covariates that explain between subject variability in eribulin PK.

Based on the previously conducted PPK analysis, a three-compartment PK model with linear elimination from the central compartment for log-transformed eribulin plasma concentration data was the starting point for the updated model.

The association between subject covariates and PK parameters was evaluated in a stepwise fashion:

- Individual Bayes posthoc pharmacokinetic parameter estimates were generated from the base model. The difference of individual estimates from the corresponding population value (η) was plotted versus the covariates to identify potential relationships.
- η-shrinkage was calculated and reported for IIV parameters estimated by the model [20]. A parameter with shrinkage greater than 30% was excluded from the covariate analysis.
- Covariates identified as being important were first assessed in the basic model by univariate addition and ranked in descending order according to the change in objective function value (OFV). All significant variables were then tested in a full model, and a subsequent backwards deletion was carried out at the 0.1% significance level where the relative influence of each covariate on the model was re-evaluated by deleting it from the full model on an individual basis.

Base Model

The PK of eribulin was best described by a three compartment model with linear elimination from the central compartment and parameterized for CL, V1, Q2, V2, Q3 and V3. An allometric model for body size effects on all of the parameters was also implemented. The use of an allometric model with body weight was found to be superior to using body surface area (BSA) effect on each of the parameters.

The estimates of PK parameters for the base model were close to those estimated from the previous analysis. For clearance (CL) IIV was estimated to be 59.3%, and 38.1% for central volume of distribution (V1). Residual variability was described by a proportional error model and the CV% was estimated to be 24.1%. The parameter estimates, precision of the estimate and 95% confidence interval for the base PK model are presented in

Table **3**.

Table 3. Population Pharmacokinetic Parameter Estimates of Eribulin Base PK Model

	NONMEM Estimates			
Parameter [Units]	**Point Estimate**	**%RSE**	**95% CI**	
CL [L/h] = Θ_{CL} *WGT$^{0.75}$	2.92	2.78	2.76 – 3.08	
V1 [L] = Θ_{V1} *WGT	4.02	2.84	3.80 – 4.24	
Q2 [L/h] = Θ_{Q2} *WGT$^{0.75}$	2.62	6.41	2.29 – 2.95	
V2 [L] = Θ_{V2} *WGT	2.42	4.71	2.20 – 2.64	
Q3 [L/h] = Θ_{Q3} *WGT$^{0.75}$	6.55	2.63	6.21 – 6.89	
V3 [L] = Θ_{V3} *WGT	121	2.59	115 – 127	
Inter-individual variability				CV%
ω^2_{CL}	0.352	9.23		59.3
ω^2_{V1}	0.145	24.0		38.1
ω^2_{Q2}	0.138	51.7		37.1
ω^2_{Q3}	0.252	10.6		50.2
ω^2_{V3}	0.138	14.9		37.1
Residual variability				CV
σ^2 prop	0.0582	13.1		24.1

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = Clearance, V1 = volume of central compartment, V2 = volume of first peripheral compartment, Q2 = inter-compartment clearance from V1 to V2, V3 = volume of second peripheral compartment, Q3 = inter-compartment clearance from V2 to V3, WGT = Weight, ω^2_{CL}, ω^2_{V1}, ω^2_{Q2}, ω^2_{Q3}, ω^2_{V3} = covariance of random effect of CL, V1, Q2, Q3 and V3, respectively, σ^2prop = proportional component of the residual error model

Co-variate model

In the univariate analysis, significant effects were seen for ALB, ALP, BILI and CLCR on CL, and these covariates were subsequently simultaneously added to the base PK model. Multivariate analysis with backward deletion resulted in a final PK model with significant effects of ALB, ALP and BILI on CL. Compared to the base PK model, the addition of the three significant covariates explained IIV on CL by 7.3 % and residual variability by 0.1 %.

The final population PK model for eribulin was a three compartment model with linear elimination from the central compartment parameterized for CL, V1, Q2, V2, Q3 and V3. IIV was estimated on all parameters except V2. A proportional error model was used for estimation of residual variability. The parameter estimates, precision of the estimate and 95% confidence interval for the final PK model are presented in

Table **4**.

Table 4. Final Model Population Pharmacokinetic Parameter Estimates of Eribulin

	NONMEM Estimates			
Parameter [Units]	**Point Estimate**	**%RSE**	**95% CI**	
$CL\ [L/h] = \Theta_{CL} * WGT^{0.75} * ALB^{\Theta ALB} * ALP^{\Theta ALP} * BILI^{\Theta BILI}$				
Θ_{CL} [L/h]	3.11	2.57	2.95 - 3.27	
Θ_{ALB} (Albumin effect on CL)	0.946	21.5	0.548 – 1.34	
Θ_{ALP} (Alkaline phosphatase effect on CL)	-0.209	17.8	-0.282 - -0.136	
Θ_{BILI} (Bilirubin effect on CL)	-0.180	29.3	-0.283 - -0.0765	
$V1\ [L] = \Theta_{V1} * WGT$				
Θ_{V1}	4.06	2.91	3.83 – 4.29	
$Q2\ [L/h] = \Theta_{Q2} * WGT^{0.75}$				
Θ_{Q2}	2.64	9.13	2.17 – 3.11	
$V2\ [L] = \Theta_{V2} * WGT$				
Θ_{V2}	2.42	4.71	2.20 – 2.64	
$Q3\ [L/h] = \Theta_{Q3} * WGT^{0.75}$				
Θ_{Q3}	6.60	2.59	6.26 – 6.94	
$V3\ [L] = \Theta_{V3} * WGT$				
Θ_{V3}	121	2.67	115 - 127	
Inter-individual variability				CV%
ω^2_{CL}	0.270	9.56		52.0
ω^2_{V1}	0.146	25.7		38.2
ω^2_{Q2}	0.139	36.0		37.3
ω^2_{Q3}	0.254	10.9		50.4
ω^2_{V3}	0.134	13.1		36.6
Residual variability				CV %
σ^2 prop	0.0577	13.3		24.0

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; CL = Clearance, V1 = volume of central compartment, V2 = volume of first peripheral compartment, Q2 = inter-compartment clearance from V1 to V2, V3 = volume of second peripheral compartment, Q3 = inter-compartment clearance from V2 to V3, ω^2_{CL}, ω^2_{V1}, ω^2_{Q2}, ω^2_{Q3}, ω^2_{V3} = covariance of random effect of CL, V1, Q2, Q3 and V3, respectively, σ^2prop = proportional component of the residual error model

Eribulin CL was identified to increase with increasing albumin (ALB) levels and decline with increasing alkaline phosphatase (ALP) and bilirubin (BILI). Similar effects of ALB and BILI were observed in the previous population PK analysis. IIV in the model parameters was moderate ranging between 36.6% for V3 and 52.0% for CL. IIV was well estimated with good precision for most parameters (%RSE ≤25.7%), however for Q2 the estimate of IIV was less precise (36.0%), but improved from the base model. The residual variability in eribulin concentrations was low (CV 24.0%).

In order to evaluate the predictive performance of the final PK model for eribulin, simulations were performed. Using parameters from the final PK model, eribulin concentrations were simulated (n = 500) following 1.4 mg/m^2 dosing on Days 1, 8 and 15 (where applicable) on each 21-days treatment cycle. The population median BSA of 1.74 m^2 was used to determine the total dose. The mean and 5th and 95th percentiles (90% PI) of these simulated concentrations were calculated and plotted with observed eribulin concentration data for dosing on Days 1, 8 and 15 (as an example, Day 15 data is shown in

Figure **1**. More than 90% of the observed eribulin concentrations for dosing on Day 1, 8 and 15 are within the 90% prediction intervals. Hence, the MAH suggests the eribulin concentration time course has been reasonably well defined by the final PK model with good predictive performance. The final PK model was also evaluated using bootstrap method (1000 replicates). The confidence intervals were generally narrow and the median values of the distribution of bootstrapped parameter values were also consistent with the original parameter estimates, for both PK structural model and covariate parameters.

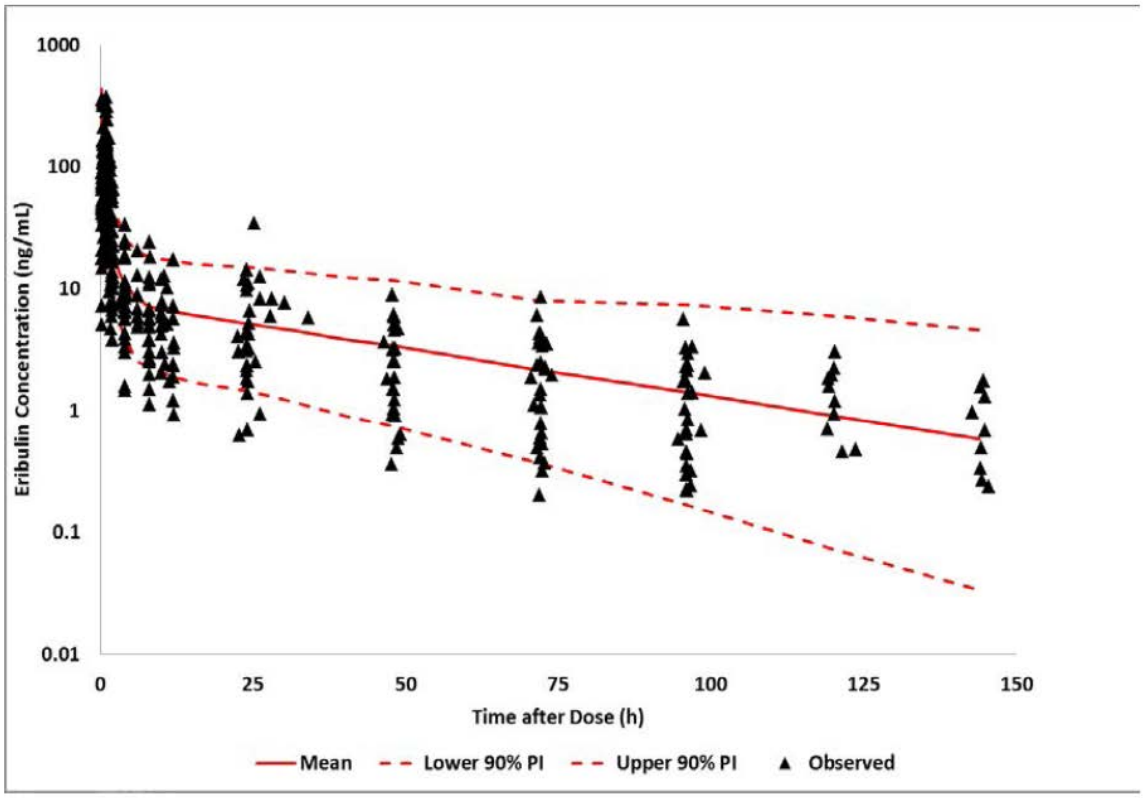

Figure 1. Visual Predictive Check of Observed and Model-Predicted Eribulin Concentrations Following 1.4 mg/m2 Eribulin Mesylate on Day 15

2.3.2.2. PK/PD Modelling

The MAH has performed a new PK/PD analysis of the relationship between eribulin plasma exposure and different efficacy or safety measures, based on data from Study 301 only. The MAH does not suggest any changes to the SmPC or other claims based on this analysis.

2.3.2.2.1. Methods

The new population PK/PD analysis was based on data from Study 301 alone, which included 9728 observations from 535 subjects.

The objectives of the population PK/PD analysis for efficacy were to

- Describe the relationship between eribulin exposure and longitudinal tumour size measurements in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes
- Identify covariates that affect eribulin exposure and longitudinal tumour size relationship

- Develop a model that relates changes in tumour size to overall survival (OS) in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes

The objectives of the population PK/PD analysis for safety were to

- Describe the relationship between neutrophil count (ANC) and eribulin concentrations in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes
- Investigate influence of patient characteristics on the development of neutropenia

In addition, exploratory PK/PD *graphical* analysis was performed to explore possible relationships between eribulin exposure and other measures of efficacy and safety.

2.3.2.2.2. Results

Tumour Growth Inhibition

The tumour-growth inhibition model included tumour growth rate (per week); tumour size reduction rate due to eribulin (per exposure per week); a resistance function; observed tumour size at baseline; and eribulin exposure (individual eribulin AUC at the time of the assessment, calculated based on dose at time of assessment and individual clearance as predicted by the population PK model). The effect of the different covariates (demographic, disease-related, previous treatment etc) was investigated one by one in a stepwise fashion as described for the PPK analysis above.

Figure 2 shows change of tumour size from baseline vs eribulin exposure (AUC) at the time of tumour measurement for those subjects in whom PK samples were collected.

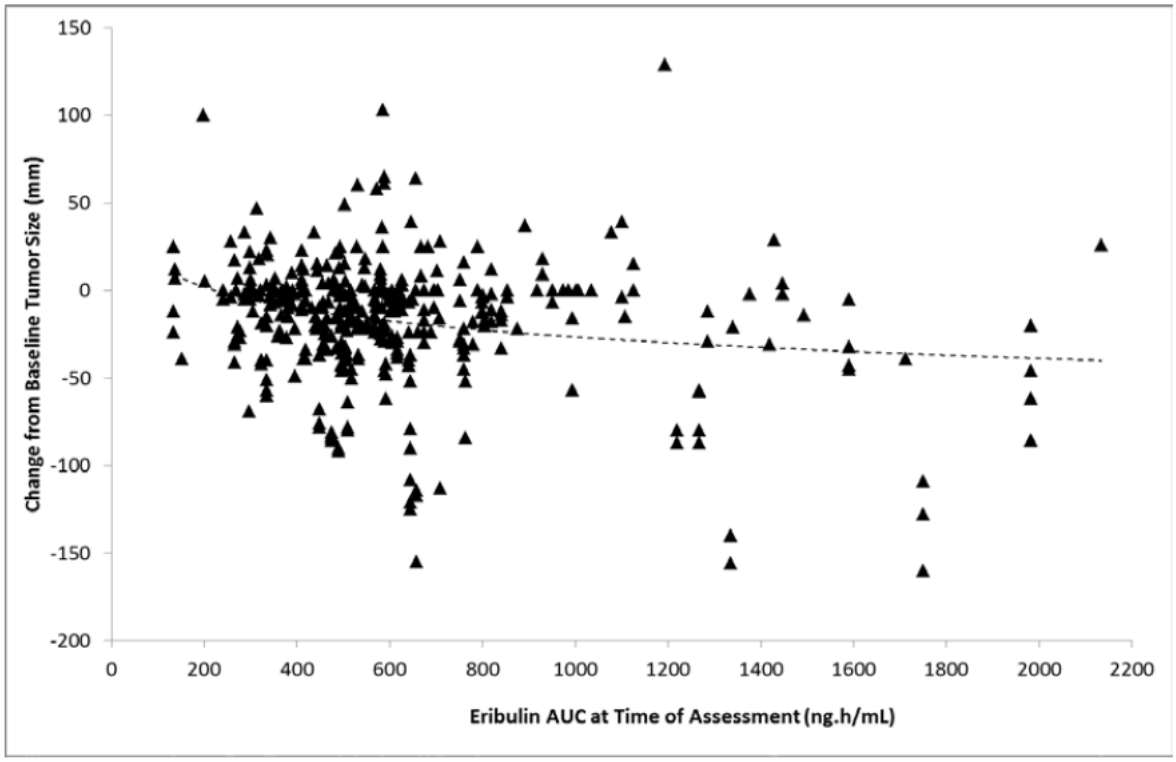

Figure 2: Change in Tumour Size from Baseline vs. Eribulin AUC at Time of Assessment

There appeared to be a slight trend towards increasing effect on tumour size with increasing eribulin exposure.

No significant co-variate could be identified.

Time-to-event analysis for Overall Survival

OS data was explored using Kaplan-Meier and Cox regression analyses. The exposure parameter used was average eribulin AUC during the study and was calculated based on the average individual dose during the study and individual PPK predicted clearance. Kaplan-Meier plots for the effect of eribulin exposure on OS (assessed in subjects with PK exposure and survival data only) are presented in the figure below.

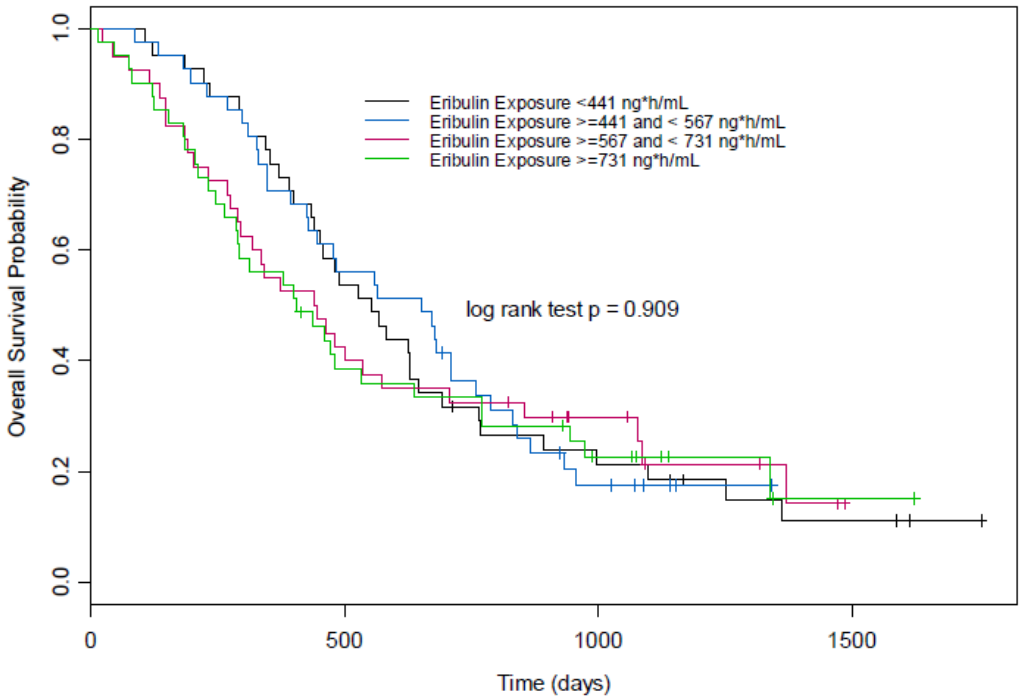

Figure 3. Kaplan-Meier Plots for OS for Eribulin Arm in Subjects with Quartiles of Eribulin Exposure (N=163, Eribulin Arm Subjects with PK Samples)

Cox regression analysis showed that eribulin exposure was a significant predictor of OS, however, Kaplan-Meier plots for OS by quartile of eribulin exposure showed no significant relationship.

Subsequent OS analysis for other possible predictors indicated that the probability of longer survival increases with a decrease in tumour size at week 6. Since decrease in tumour size appeared to be related to eribulin exposure (see above), the MAH suggests that this indicates an indirect eribulin exposure relationship with OS.

Eribulin/Neutropenia

The relationship between eribulin concentrations and absolute neutrophil count (ANC) was described using a semi-physiological PK/PD model for haematological toxicity. Eribulin concentration at the time of ANC assessment was predicted using the final population PK model. The effect of different covariates was assessed as described above. Due to the very long run time when using FOCE, the FO estimation method was used. The effect of different co-variates was investigated one by one in a stepwise fashion. The parameter estimates for the base neutropenia PK/PD model are presented in Table 5.

Table 5. Population Parameter Estimates for Neutropenia Base PK/PD Model

	NONMEM Estimates			
Parameter [Units]	**Point Estimate**	**%RSE**	**95% CI**	
BASE [IU/L]	3.70	1.68	3.58 - 3.82	
MTT [h]	108	1.62	105 - 111	
GAMMA	0.231	1.90	0.222 - 0.240	
SLOPE [mL/ng]	0.0406	3.52	0.0378 - 0.0434	
Inter-individual variability (ω^2)				CV%
ω^2BASE	0.0789	9.15		28.1
ω^2MTT	0.0212	18.9		14.6
ω^2GAMMA	0.0229	35.0		15.1
ω^2SLOPE	0.196	26.5		44.3
Residual variability (σ^2)				CV%
σ^2 prop	0.140	4.85		37.4

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100; BASE = Baseline absolute neutrophils, MTT=Neutrophil maturation time, γ = Feedback parameter, SLOPE = Slope relating eribulin concentrations to decreased neutrophil proliferation, ω^2_{BASE}, ω^2_{MTT}, ω^2_{GAMMA}, ω^2_{SLOPE} = covariance of random effect of BASE, MTT, GAMMA and SLOPE, respectively, σ^2prop = proportional component of the residual error model

Parameters were estimated with good precision with %RSE less than 4%. Diagnostic plots for the base PK/PD model (indicated that the model adequately described the observed neutrophil levels following eribulin administration.

Multivariate analysis with backward deletion resulted in the following significant covariates:

- neutropenia medication [G-SCF)] (NEUTM) on baseline absolute neutrophils (BASE)
- NEUTM, ALP and bilirubin (BILI) on neutrophil maturation time (MTT)
- Weight on the feed-back parameter for ANC (Gamma)
- NEUTM and ALP on the eribulin effect on ANC (SLOPE)

The diagnostic plots for the final model indicated that the PK/PD model adequately described ANC data with no systematic bias in the predictions.

2.3.2.3. Physiologically-based pharmacokinetic modelling (PBPK)

Eribulin has previously been shown to inhibit CYP3A4 in vitro, but there is no data on the effect of eribulin on CYP3A4 substrates in vivo. To explore the potential for a clinical drug-drug interaction between eribulin and midazolam, a physiologically based pharmacokinetic (PBPK) model was built using a commercially available program. The parameters used to build the model were generated from both in vitro and in vivo experiments (bottom-up plus top-down). Some of the parameters were predicted by in silico methods. The model was used to simulate the effect of 1.4 mg/m2 eribulin mesilate disposition on exposure of co-administered midazolam, a model CYP3A4 substrate. In an additional simulation, a supra-therapeutic 3.0 mg/m2 dose of eribulin mesylate was used as a “worst case” scenario. Simulations were conducted for 10 groups of 10 patients for a total of 100 patients for each eribulin dose (for details, refer to the Response Assessment Report).

The results of the simulation are presented in the table below.

Table 6: Summary Statistics for the Model-Predicted AUC Values of Midazolam for Drug-drug Interaction Simulations with Eribulin

Eribulin Mesilate Dose (mg/m^2)	Midazolam Dose (mg)	AUC_{Ratio} Geom. mean	95% CI	AUC_{Ratio} Median	AUC_{Ratio} Max	AUC_{Ratio} Min
1.4	2.0	1.0137	1.0029 - 1.0144	1.0143	1.0220	1.0032
3.0	2.0	1.0292	1.0276 - 1.0308	1.0304	1.0469	1.0068

AUC_{Ratio}: ratio between the area under the concentration versus time curve (AUC) of midazolam in the absence and presence of eribulin.
AUC = area under the curve, CI = confdence interval, Max = maximum, Min = minimum

The geometric mean AUC ratio for midazolam 2 mg PO with and without eribulin mesilate 1.4 mg/m2 was roughly 1.01. The geometric mean AUC ratio after the supra-therapeutic 3.0 mg/m2 eribulin mesilate dose was roughly 1.03.

Sensitivity analysis for the effect of different CYP3A4 Ki values of eribulin on the predicted AUC ratio was performed. The result of this analysis indicates that the interaction risk between midazolam and eribulin is negligible (less than 15% increase in midazolam exposure) even at Ki values 10-fold lower than the ones determined from the in vitro inhibition studies.

Thus, this simulation study indicates that eribulin is not a clinically relevant inhibitor of CYP3A4.

Sensitivity analyses have been performed with simulations using e.g. an increased dose (increased exposure) of eribulin, by changing Ki, and by decreasing Ki to reflect a higher liver concentration of eribulin (the latter analysis was made by the assessor). With a higher liver concentration, as indicated from data on the ratio between blood and liver concentration in the rat, the predicted AUC ratio for midazolam with/without eribulin was 1.27, i.e. slightly above the 1.25 limit normally used to exclude a significant interaction.

2.3.3. Discussion on clinical pharmacology

With the current variation, the MAH has provided an updated PPK model and a PK/PD analysis, but proposes no new claims or SmPC changes based on these analyses, which is considered appropriate.

Inclusion of data from the new phase III study 301 in the PPK model did not add information or change previous conclusions on eribulin pharmacokinetics. Pharmacokinetic data from Japanese patients is limited, but the PPK analysis indicated no obvious difference in exposure between Japanese and other races that could explain the observed increased frequency of neutropenia in Japanese patients.

The PK/PD analyses indicated a relationship between eribulin exposure and tumour size as well as between eribulin exposure and neutrophil count. The identified co-variates for neutropenia were, however, not predictive of the risk of developing grade 3/4 neutropenia. Early identification of patients at high risk for grade 3/4 neutropenia using the PK/PD model and covariate values is thereby not possible. The PK/PD analyses have no major implications for approval of the new indication.

The recommendations for drug-drug interactions given in the SmPC are updated with this application. Eribulin is eliminated primarily via biliary excretion of unchanged compound into faeces, but the transporters involved have not yet been identified. The current SmPC contains relatively wide warnings that concomitant use of transporter inhibitors is not recommended. The MAH is in the process of identifying the transporters involved in eribulin elimination and performing a new in vitro induction study in accordance with the recommendations in the new CHMP Guideline on the Investigation of Drug Interactions and relevant revisions through an on-going procedure EMEA/H/C/002084/II/0014 are under evaluation by the CHMP. These changes are important also in view of the expansion of the target population.

Eribulin showed inhibition of CYP3A4 in vitro, but whether it is a clinically relevant inhibitor of CYP3A4 is not known. The MAH therefore made simulations using a physiologically-based pharmacokinetic (PBPK) model, in order to predict the effect of eribulin on the sensitive CYP3A4 substrate midazolam. The PBPK modelling approach is generally agreed, and overall the PBPK model predicts reasonably well eribulin pharmacokinetics. Relevant sensitivity analyses were performed. The results of the simulations indicated that although the risk for an effect of eribulin on a sensitive CYP3A4 substrate cannot be completely excluded, eribulin would be at most considered a mild CYP3A4 inhibitor.

The PBPK model prediction is considered sufficient to be used as a basis to update the SmPC recommendation, and a clinical interaction study with midazolam will not be considered necessary. In the SmPC, a warning of caution at concomitant administration of drugs that are sensitive CYP3A4 substrates and that have a narrow therapeutic index has been included.

2.3.4. Conclusions on clinical pharmacology

The updated PPK model, with addition of data from Study 301, and a new PK/PD model including data from study does not alter the conclusion drawn on eribulin pharmacokinetics as compared with the previous PPK model, included in the original MAA. Results of the PK/PD modelling do not have implications for the benefit/risk assessment of the currently applied indication.

2.4. Clinical efficacy

2.4.1. Main study

Study 301

Protocol 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"

Methods

Study 301 was a Phase 3, multicenter, open-label, randomized, two-parallel-group study in patients with locally advanced or metastatic breast cancer. The trial was performed at 210 sites across six geographic regions (North America, Western Europe, Eastern Europe, Latin America, South Africa and Asia). Number of subjects, planned = 1100; enrolled = 1102. (Eribulin 554, capecitabine 548.)

Table 7. Description of Study 301

Study ID	No. of Study Centers (Location)	Study Start / Data Cut Off Date	Study Design Control Type	Study Dose, Route & Regimen	No. Subjects Entered / No. Deaths / No. Still Receiving Treatment	Sex (M/F) Median Age (y) (Range)	Diagnosis Inclusion Criteria	Primary Efficacy Endpoints
E7389-G000-301	210 (North America, Latin America, Europe, Asia, South Africa, and Australia)	01 Apr 2006 / 12 Mar 2012	Phase 3, randomized, open-label, parallel group; prestratified based on geographic region and HER2 status Active control	Eribulin mesilate 1.4 mg/m^2 Capecitabine 2.5 g/m^2/day Eribulin i.v. bolus over 2 to 5 minutes on Days 1 and 8 of each 21-day cycle until disease progression. Capecitabine administered p.o. twice daily in 2 equal doses on Days 1 to 14 each 21-day cycle.	Total: 1102 / 905 / 10 Eribulin: 554 / 446 / 5 Capecitabine: 548 / 459 / 5	Total: 0M / 1102F 54.0 (24-80) Eribulin: 0M / 554F 54.0 (24-80) Capecitabine: 0M / 548F 53.0 (26-80)	Females age ≥18 years 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.	OS, PFS

Source: SCE, Table 1.

Study participants

Eligibility criteria

Breast cancer subjects who had received up to three prior chemotherapy regimens, and no more than two prior regimens for advanced and/or metastatic disease. The chemotherapy regimens must have included an anthracycline and a taxane, either in the (neo) adjuvant setting or for locally advanced or metastatic disease. Subjects enrolled into the study had documented evidence of disease progression during or after their most recent anticancer therapy.

In addition, subjects with known human epidermal growth factor receptor 2 (HER2/neu) overexpressing tumours could have been previously treated with trastuzumab in study centres where this treatment was available, and subjects with known oestrogen receptor (ER) and/or progesterone receptor (PR) positive disease may have been treated with hormonal therapy, but not required per protocol. Subjects for whom HER2/neu status, oestrogen receptor (ER), and progesterone receptor (PR) status were unknown were also accepted into the study.

The difference in inclusion criteria compared with the already approved indication is the required number of prior chemotherapy regimens for advanced disease: 0 in this study compared with 2 in the registration Study 305.

The full list of inclusion and exclusion criteria is given below.

Table 8. Inclusion and exclusion criteria of Study 301

Inclusion Criteria	*Exclusion Criteria*
1. Female subjects with histologically or cytologically confirmed carcinoma of the breast. 2. Subjects with locally advanced or metastatic disease who had 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 anticancer therapy, and this was to be documented • Patients with known HER2/neu over-expressing tumours (see Section 11.1.2 of the Clinical Protocol, included in Appendix 16.1.1 of this report) could have additionally been treated with trastuzumab in centres where this treatment was available • Patients with known oestrogen and/or progesterone receptor-expressing tumours could have been additionally treated with hormonal therapy 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	1. Received more than three prior chemotherapy regimens for their disease, including adjuvant therapies, or who received more than two prior chemotherapy regimens for advanced disease (other therapies are allowed e.g., anti-estrogens, trastuzumab and radiotherapy) 2. Received capecitabine as a prior therapy for their disease 3. Received chemotherapy, radiation, or biological therapy within 2 weeks, or hormonal therapy within 1 week before study treatment start, or any investigational drug within 4 weeks before study treatment start 4. Radiation therapy encompassing > 30% of marrow 5. Prior treatment with mitomycin C or nitrosourea 6. Pulmonary lymphangitic involvement that resulted in pulmonary dysfunction requiring active treatment, including the use of oxygen 7. Subjects with brain or subdural metastases were not eligible, unless they completed local therapy and discontinued the use of corticosteroids for this indication for at least 4 weeks before starting study treatment. Any symptoms attributed to brain metastases must have been stable for at least 4 weeks before starting study treatment; radiographic stability was to 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. Subjects with meningeal carcinomatosis 9. Subjects who were receiving anticoagulant therapy with

5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1 or 2 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 8. Adequate bone marrow function as evidenced by absolute neutrophil count (ANC) ≥ 1.5 × 109/L, haemoglobin ≥ 10.0 g/dL (a haemoglobin <10.0 g/dL was acceptable if it was corrected by growth factor or transfusion), and platelet count ≥ 100 × 109/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 × ULN (in the case of liver metastases ≤ 5 × ULN), or in case of bone metastases, liver specific alkaline phosphatase ≤ 3 × ULN 10. Subjects willing and able to complete the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) with breast cancer module QLQ-BR23 and Pain VAS 11. Subjects 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 subject could withdraw consent at any time without prejudice	warfarin or related compounds, other than for line patency, and could not be changed to heparin-based therapy, were not eligible. If a subject was to continue on mini-dose warfarin, then the prothrombin time (PT) / international normalized ratio (INR) was to be closely monitored 10. Women who were 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 have been a barrier method, e.g., condom, diaphragm, or cervical cap). Perimenopausal women were to be amenorrheic for at least 12 months to be considered of nonchildbearing potential 11. Severe/uncontrolled intercurrent illness/infection 12. Significant cardiovascular impairment (history of congestive heart failure New York Heart Association (NYHA) > Grade II, unstable angina or myocardial infarction within the past six months, or serious cardiac arrhythmia) 13. Subjects with organ allografts that required immunosuppression 14. Subjects with known positive HIV status 15. Subjects who 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. Subjects with neuropathy > Grade 2 at screening 17. Subjects with a hypersensitivity to halichondrin B and/or halichondrin B chemical derivative 18. Subjects who participated in a prior eribulin clinical trial, or 19. Subjects with other significant disease

*: Any single-agent therapy, and any combination of cytotoxic, hormonal, biological targeted agents, and/or humanized antibodies, scheduled to be administered as a preplanned treatment, given concomitantly, sequentially, or both, was considered one regimen. Planned neoadjuvant chemotherapy (to debulk the tumour prior to surgical intervention) plus postoperative adjuvant chemotherapy was also considered one regimen. If, due to toxicity, the dosing of one or more of the components had to be reduced, or one or more of the components of the regimen was to be omitted, or one of the components was to be replaced with another similar drug, the changed version of the original regimen was not considered a new regimen. However, if a new component dissimilar to any of the original components was added to the regimen, the new combination was considered a new regimen.Prior hormonal therapy, biological therapy (e.g., trastuzumab, bevacizumab), or immunotherapy was not to be counted as one of the prior chemotherapy regimens allowed. However, hormonal therapy was discontinued 1 week before administration of study treatment, and biological therapy was discontinued 2 weeks before study treatment administration. If the treatment was interrupted for surgery or radiotherapy and then continued with an unchanged schedule and components, that treatment was considered as one regimen despite the interruption.

Treatments

Subjects were randomized in a ratio of 1:1 to receive either the test drug eribulin as an intravenous (IV) infusion of 1.4 mg/m^2 over 2-5 minutes on Days 1 and 8 every 21 days; or the comparator drug capecitabine as an oral administration of 2500 mg/m^2/day administered twice daily in two equal doses on Days 1 to 14 in each 21-day cycle.

Subjects continued on treatment until unacceptable toxicity, progression of disease, or until in the opinion of the investigator, discontinuation of therapy was in the best interest of the subject or the subject withdrew consent. Subjects who demonstrated clinical benefit were allowed to continue treatment for as long as clinical benefit was sustained.

Objectives

Primary: To compare the efficacy of eribulin versus capecitabine monotherapy in terms of overall survival (OS) and progression-free survival (PFS) in subjects with locally advanced or metastatic breast cancer.

Secondary: Quality of life (QoL), objective tumour response rate (ORR), duration of response (DoR), 1-, 2-, and 3-year survival, tumour-related symptom assessments, safety, investigation of pharmacokinetic/pharmacodynamics (PK/PD) relationships in a population PK study following administration of eribulin in approximately 200 subjects.

Outcomes / endpoints

Primary endpoints

Overall Survival

Overall survival was measured from the date of randomization until date of death from any cause or the last date the subject was known to be alive.

Progression-Free Survival

Progression-Free Survival was measured from the date of randomization to the date of recorded progression of the disease or the death of the subject from any cause, whichever occurred first.

Tumour response data utilized in the main analysis of PFS was obtained from an independent review of the imaging scans.

Secondary endpoints

• Quality of Life measured using the EORTC questionnaire (QLQ-C30 BR23)

• Objective tumour response rate as measured using RECIST

• Duration of response

• One-, two-, and three-year survival

• Tumour related symptom assessments measured by pain intensity, using a VAS, and analgesic consumption.

• Safety parameters (adverse events, laboratory parameters, concomitant medication, and study drug exposure)

• Population PK in the eribulin group

Efficacy assessments

Baseline tumour assessments, consisting of computed tomography (CT) or magnetic resonance imaging (MRI) scans of areas of suspected disease, as well as photographs of skin lesions, were performed within 28 days prior to starting study treatment and every second cycle (starting at Cycle 2) for the first 12 cycles, then every third cycle (starting at Cycle 15) between Days 15 and 21, or sooner if there was evidence of disease progression. Tumour response was to 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.

Quality of Life assessments

Subjects assessment of QoL was evaluated using the EORTC questionnaire (QLQ-C30, plus breast module BR23) at Baseline and at 6 weeks, 3 months, and then at 6-month intervals after the start of study treatment. Tumour-related symptom assessments, based on the change from Baseline in pain intensity, were recorded by the subject at Baseline (within 7 days of Day 1 Cycle 1) and weekly during the study using a VAS, and consumption of analgesic medications were recorded at Baseline and throughout the study. Eastern Cooperative Oncology Group (ECOG) performance status was assessed at Baseline, Day 1 of every cycle, and at Study Termination.

Sample size

A total of 1100 subjects (550 subjects per group) were planned for enrolment into the study.

Subjects were randomized to treatment with either E7389 or capecitabine in a ratio of 1:1. Randomization was prestratified based on the geographic region and HER-2/neu status. To avoid a centre effect, any one centre could enrol a maximum of only 5% of the total study population (i.e., 55 subjects).

The sample size calculation was 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 was 905, an overall 0.04 level two-sided log rank test had approximately 90% power to detect a difference between the two survival curves if the alternative hypothesis hazard ratio was 0.80 (a 3-month increase in median survival over the 12-month median survival of capecitabine). To account for censoring in the study, a total of 1100 randomized subjects was planned.

Randomisation

Subjects were pre-stratified based on geographic region and HER-2/neu status (positive, negative, or unknown), and then randomised to one of the two treatment groups within each stratum in a 1:1 ratio to either E7389 or capecitabine.

Blinding (masking)

This was an open-label study. However, the Eisai study statistical team was blinded to dosing data and treatment group assignment until database lock to avoid potential bias. Independent statisticians conducted the interim analyses and assisted with queries.

Statistical methods

The study was to be declared positive after achievement of any of the following outcomes for OS:

1. First interim analysis after 453 deaths: OS of eribulin was statistically significantly better compared to capecitabine ($P \leq 0.002$).
2. Second interim analysis after 603 deaths: OS of eribulin was statistically significantly better compared to capecitabine ($P \leq 0.0081$).
3. Final analysis after 905 deaths: OS of eribulin was statistically significantly better compared to capecitabine ($P \leq 0.0372$).
4. Final analysis after 905 deaths: OS hazard ratio (eribulin/capecitabine) was < 1 and PFS of eribulin was statistically significantly better compared to capecitabine ($P \leq 0.01$).

Decisions were based on two-sided, stratified log-rank tests with HER2/neu status[1] and geographic region as strata. The overall significance level alpha of 0.05 was adjusted for the two primary endpoints: 0.04 was used for testing OS, and 0.01 was used for testing PFS.

OS was measured from the date of randomization until the date of death from any cause. Subjects who were lost to follow-up or who were alive at the date of data cut-off were censored. To maintain an overall level of 0.04, alpha spending for sequential analyses of OS was based on the Lan−DeMets implementation of the O'Brien−Fleming spending function. The P value boundaries of 0.002, 0.0081, and 0.0372 are examples when the observed number of deaths at the times of interim analyses (453, 603, and 905 deaths, respectively).

Hypotheses tested included:

H_a: S(eribulin) = S(capecitabine)

H_a: S(eribulin) $\neq$ S(capecitabine)

where S is the survival distribution of OS.

PFS was compared between the two treatment groups using a two-sided 0.01 level stratified log-rank test. Hazard ratio (eribulin/capecitabine) was provided 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 according to IVRS data. Median and 95% CI were provided using Kaplan−Meier estimate and Greenwood formula for each treatment group. PFS was plotted using Kaplan−Meier estimate. 6- and 12-month PFS rates were provided using Kaplan−Meier method together with 95% CI.

Additional exploratory Cox regression analysis was performed adjusting for the covariates. In addition to the censoring rules the Independent Review Charter described the rules for handling certain missing data.

The censoring rules for the primary analysis of PFS were according to FDA guidance in 2007.

Sensitivity analysis #1: PFS endpoint was analysed according to EMEA guideline on the methodological considerations for using PFS as primary endpoint in confirmatory trials for registration. This included that progression/death events were counted as events and not censored even in cases where they occurred after discontinuation (for other than progressive disease), after start of new anticancer treatment, or after two or more missed tumour assessments.

Sensitivity analysis #2: PFS endpoint was determined and analyzed using the investigator's disease assessments and also considered symptomatic progression as an event.

[1] There were 70 (6.35%) subjects whose HER2/neu status was incorrectly entered into the IVRS database at time of randomization as determined by source document verification leading to the final, locked clinical database. Given this discordance, according to the SAP, the log-rank test stratified by geographic region and verified HER2/neu status in the clinical database was used.

Objective Response Rate (ORR) was defined as the number of subjects with best overall response of complete response (CR) or partial response (PR) divided by the number of subjects in the analysis population. The response rate was based on the independent review of disease assessments and investigator's assessments. Subjects with unknown or missing response were treated as non-responders, i.e., they were included in the denominator when calculating percentages. Response rate was compared between the two groups using the Cochran-Mantel- Haenszel test with adjustment of stratification factors geographic region and HER2/neu status. If the test was not feasible or unreliable due to the large number of strata relative to the number of responders, Fisher's exact test was used. Response rate was summarized by treatment group with the 95% CI using Clopper–Pearson method.

Tumour response was evaluated according to the modified RECIST guidelines. The response assessment categories were CR, PR, Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE). The best overall response was the best response achieved during the study. CRs and PRs were to be confirmed by a repeat assessment of response (CR or PR) separated by at least 4 weeks (28 days). In the case of SD, post-treatment measurement must have met the SD criteria at least once after the first drug administration at a minimum interval of 5 weeks (35 days). CR or PR assessed a minimum of 5 weeks (35 days) after start of treatment with a subsequent PD will be considered SD for the best response. However, CR or PR assessed less than 5 weeks (35 days) from start of treatment with a subsequent PD was considered PD for the best response.

Tumour response was independently reviewed by the imaging company, Radpharm, Inc. Best overall response for the investigators' assessments was derived programmatically based on the response assessments at each visit.

Duration of Response (DoR) (days) = Date of progression/ death/ censoring – Date of first documented CR or PR +1.

The primary QoL analysis will focus on the global health status/QoL (questions 29 and 30) at week 6. The difference in global health status/QoL scores at week six between the treatment arms will be compared using a Wilcoxon Rank-Sum test.

Results

Participant flow – subject disposition

Table 9. Subject Disposition and Primary Reason for Discontinuation From Study Treatment: All Randomized Subjects

	Treatment Groups		Total
	E7389	Capecitabine	
All screened subjects [a]			1276
Randomized, n	554	548	1102
Not treated, n (%)	10 (1.8)	2 (0.4)	12 (1.1)
Treated, n (%)	544 (98.2)	546 (99.6)	1090 (98.9)
Survival status at date of data cutoff [b]			
Alive, n (%)	87 (15.7)	65 (11.9)	152 (13.8)
Dead	446 (80.5)	459 (83.8)	905 (82.1)
Subject withdrew consent	12 (2.2)	9 (1.6)	21 (1.9)
Lost to follow-up	9 (1.6)	15 (2.7)	24 (2.2)
Number of subjects on treatment after data cutoff	5 (0.9)	5 (0.9)	10 (0.9)
Discontinued study, n (%)	549 (99.1)	543 (99.1)	1092 (99.1)
Primary reason for discontinuation, n (%)			
Progression of disease [c]	409 (73.8)	405 (73.9)	814 (73.9)
Adverse event [d]	45 (8.1)	59 (10.8)	104 (9.4)
Subject choice [e]	34 (6.1)	27 (4.9)	61 (5.5)
Clinical progression	27 (4.9)	24 (4.4)	51 (4.6)
Physician's decision	15 (2.7)	14 (2.6)	29 (2.6)
Subject withdrew consent	8 (1.4)	5 (0.9)	13 (1.2)
Other	5 (0.9)	6 (1.1)	11 (1.0)
Entry criteria not met	4 (0.7)	1 (0.2)	5 (0.5)
Lost to follow-up	1 (0.2)	2 (0.4)	3 (0.3)
Death	1 (0.2)	0 (0.0)	1 (0.1)
Death during study or within 30 days of last dose	26 (4.7)	36 (6.6)	62 (5.6)

Note: Percentages are based on the number of subjects randomized in relevant treatment group.

a: All subjects who signed informed consent.

b: Date of data cutoff 12 Mar 2012.

c: Progressive disease assessed using Response Evaluation Criteria in Solid Tumors (RECIST).

d: Four subjects discontinued due to an AE, although the AE leading to discontinuation was recorded more than 30 days after the last dose of study drug.

e: Subject agreed to survival follow-up assessments.

Source: Study 301 CSR, Table 7.

Recruitment

Start date 01 Apr 2006. At the date of data cut-off (12 Mar 2012), 10 subjects (5 subjects [0.9%] each in the eribulin and capecitabine groups) were still on treatment. The trial was performed at 210 sites across six geographic regions.

Conduct of the study

Protocol amendments

The original protocol was issued on 17 November 2005. Seven amendments were made to the protocol and a final protocol was issued on 03 March 2009.

The main changes (according to assessor) are shown below:

Amendment 01, 14 Dec 2005

- PFS was changed from a secondary objective to a primary objective.

Amendment 02, 02 Mar 2006:

- Trastuzumab was not available at all study centres; therefore, the requirement for previous exposure to trastuzumab was modified to allow subjects to participate in the study without previous exposure to trastuzumab.
- As PFS was made a primary endpoint, independent review of scans were to be performed.

Amendment 04, 05 Dec 2006:

- Eligibility criteria regarding prior chemotherapy were changed to include a more complete representation of the breast cancer population: "Patients with locally advanced or metastatic breast cancer who have received one or two prior chemotherapy regimens" was changed to: "…who have received up to three prior chemotherapy regimens, and no more than two prior regimens for advanced disease."

Amendment 06, 06 Mar 2008:

- Allowed investigator more discretion for dose reductions of capecitabine on the first instance of Grade 2 toxicity, reflecting current medical practices. The following footnote was added to dose modification table for capecitabine: "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."

- ***Protocol violations***

The most common violations were violations of inclusion criterion #2 and exclusion criterion #1 (7 subjects each) that required subjects to have received up to three prior chemotherapy regimens and no more than two prior regimens for advanced and/or metastatic disease.

Table 10. Reason for Exclusion from the Per Protocol Population: ITT Population

	Treatment Groups		Total
	E7389	Capecitabine	
Subjects excluded from Per Protocol population	33 (6.0)	41 (7.5)	74 (6.7)
Randomized but not dosed	10 (1.8)	2 (0.4)	12 (1.1)
Subjects who did not receive a full cycle of study drug	9 (1.6)	21 (3.8)	30 (2.7)
Subjects who had major protocol violations	17 (3.1)	21 (3.8)	38 (3.4)
Concomitant treatments not permitted [a]	2 (0.4)	0	2 (0.2)
Patients missing baseline tumor assessment	6 (1.1)	5 (0.9)	11 (1.0)
Study entry criteria	9 (1.6)	16 (2.9)	25 (2.3)
Inclusion Criteria: 2	4 (0.7)	3 (0.5)	7 (0.6)
Inclusion Criteria: 9	0	1 (0.2)	1 (0.1)
Exclusion Criteria: 1	4 (0.7)	3 (0.5)	7 (0.6)
Exclusion Criteria: 5	0	2 (0.4)	2 (0.2)
Exclusion Criteria: 6	0	1 (0.2)	1 (0.1)
Exclusion Criteria: 7	1 (0.2)	4 (0.7)	5 (0.5)
Exclusion Criteria: 8	0	1 (0.2)	1 (0.1)
Exclusion Criteria: 12	0	1 (0.2)	1 (0.1)

a: Determined as protocol violation criteria

Source: Study 301 CSR, Table 8. Keywords for inclusion (InC) and exclusion criteria (ExC) are given below. For a full description please refer to the list on p. 22.

InC-2 and ExC-1: Maximum 3 prior chemotherapy regimens, max 2 for advanced disease. Inc-9: Adequate liver function. ExC-5 Prior mitomycin C or nitrosourea, ExC-6 Pulmonary lymphangitic involvement, ExC-7 brain or subdural metastases, ExC-8 meningeal carcinomatosis, ExC-12 cardiovascular impairment.

Baseline data

Demographics

Table 11. Baseline Demographics: ITT Analysis Set

Category	Treatment Groups		
	E7389 (N=554)	Capecitabine (N=548)	Total (N=1102)
Age (year)[a]			
N	554	548	1102
Mean (SD)	53.8 (10.37)	52.8 (10.20)	53.3 (10.29)
Median	54.0	53.0	54.0
Min, Max	24, 80	26, 80	24, 80
Age group (years), n (%)			
≤ 40	59 (10.6)	73 (13.3)	132 (12.0)
40 to < 55	220 (39.7)	234 (42.7)	454 (41.2)
≥ 55 to < 65	179 (32.3)	179 (32.7)	358 (32.5)
≥ 65 to < 75	89 (16.1)	53 (9.7)	142 (12.9)
≥ 75	7 (1.3)	9 (1.6)	16 (1.5)
Race, n (%)			
White	496 (89.5)	495 (90.3)	991 (89.9)
Black or African American	15 (2.7)	16 (2.9)	31 (2.8)
Asian / Pacific Islander	18 (3.2)	18 (3.3)	36 (3.3)
Other	25 (4.5)	19 (3.5)	44 (4.0)
ECOG performance			
0	250 (45.1)	230 (42.0)	480 (43.6)
1	293 (52.9)	301 (54.9)	594 (53.9)
2	11 (2.0)	16 (2.9)	27 (2.5)
3	--	1 (0.2)	1 (0.1)

Source: Study 301 CSR, Table 10.

Additional medians at baseline in the eribulin and capecitabine arms, respectively (ITT set):

Weight 69.0 and 70.0 kg; age 54.0 and 53.0 years; weight 69.0 and 70.0 kg; height160.0 and 161.0 cm; BMI 26.7 and 27.0 kg/m^2; BSA 1.74 and 1.75 m^2. (Source: Study 301 CSR, Table 10).

Disease Characteristics

Time since original diagnosis was somewhat higher in the eribulin arm, 36 months vs. 31 months (

Table **12**). HER2 positivity was approximately 15% in both study arms. Oestrogen receptor (ER) and hormone receptor (HR) positivity were somewhat lower (approximately 4%), and triple negativity slightly higher (2.6%) in the eribulin arm compared with the capecitabine arm.

Table 12. Disease Characteristics: ITT Analysis Set

Category	Treatment Groups		Total (N=1102)
	E7389 (N=554)	Capecitabine (N=548)	
Time since original diagnosis (months)			
Mean (SD)	52.2 (49.2)	46.1 (43.6)	49.1 (46.6)
Median	36.0	31.0	33.0
Min, max	2, 339	2, 259	2, 339
Age at diagnosis (years)			
Mean (SD)	49.5 (10.20)	49.0 (10.19)	49.2 (10.19)
Median	49.0	49.0	49.0
Min, max	23, 78	25, 79	23, 79
Diagnosis of malignant disease, n (%)			
Ductal adenocarcinoma,	390 (70.4)	399 (72.8)	789 (71.6)
Lobular adenocarcinoma	53 (9.6)	39 (7.1)	92 (8.3)
Other	111 (20.0)	110 (20.1)	221 (20.1)
Stage at diagnosis, n (%)			
I	23 (4.2)	40 (7.3)	63 (5.7)
II	220 (39.7)	176 (32.1)	396 (35.9)
III	207 (37.4)	219 (40.0)	426 (38.7)
IV	87 (15.7)	96 (17.5)	183 (16.6)
Missing	17 (3.1)	17 (3.1)	34 (3.1)
Tumor grade at diagnosis, n (%)			
1	39 (7.0)	26 (4.7)	65 (5.9)
2	201 (36.3)	214 (39.1)	415 (37.7)
3	173 (31.2)	178 (32.5)	351 (31.9)
4	1 (0.2)	0 (0.0)	1 (0.1)
Missing	140 (25.3)	130 (23.7)	270 (24.5)

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HER2/*neu* Status (CRF), n (%)				
IHC	0	248 (44.8)	237 (43.2)	485 (44.0)
	1+	79 (14.3)	97 (17.7)	176 (16.0)
	2+	39 (7.0)	43 (7.8)	82 (7.4)
	3+	82 (14.8)	73 (13.3)	155 (14.1)
	Not done	106 (19.1)	98 (17.9)	204 (18.5)
FISH	positive	19 (3.4)	22 (4.0)	41 (3.7)
	negative	63 (11.4)	54 (9.9)	117 (10.6)
	not done	472 (85.2)	472 (86.1)	944 (85.7)
Overall	positive	86 (15.5)	83 (15.1)	169 (15.3)
	negative	375 (67.7)	380 (69.3)	755 (68.5)
	not done	93 (16.8)	85 (15.5)	178 (16.2)
ER status	positive	259 (46.8)	278 (50.7)	537 (48.7)
	negative	233 (42.1)	216 (39.4)	449 (40.7)
	not done	62 (11.2)	54 (9.9)	116 (10.5)
PR status	positive	227 (41.0)	234 (42.7)	461 (41.8)
	negative	262 (47.3)	248 (45.3)	510 (46.3)
	not done	65 (11.7)	66 (12.0)	131 (11.9)
Hormone receptor status	positive	279 (50.4)	305 (55.7)	584 (53.0)
	negative	212 (38.3)	184 (33.6)	396 (35.9)
	unknown	63 (11.4)	59 (10.8)	122 (11.1)
Triple negative (HER2/*neu*–, ER–, PR–)		150 (27.1)	134 (24.5)	284 (25.8)

CRF = case report form, ER = estrogen receptor, FISH = fluorescence in situ hybridization, HER2/*neu* = human epidermal growth factor receptor 2, IHC = immunohistochemical, ITT = intent-to-treat, Max = maximum, Min = minimum, PR = progesterone receptor, SD = standard deviation.

Source: Study 301 CSR, Table 11. Assessor's note: The HER2 status" Overall" is based on the clinical database.

Tumour sites and number of organs involved were overall similar across study arms, although the capecitabine group had approximately 5% more patients with liver metastases and 4% less patients with only 1 organ involved (Table 13).

Table 13. Baseline disease sites, Study 301

Parameter		E7389 (N=554) n	(%)	Capecitabine (N=548) n	(%)	Total (N=1102) n	(%)
Tumour Sites	CNS (Brain/Spine)	4	(0.7)	4	(0.7)	8	(0.7)
	Bone	299	(54.0)	308	(56.2)	607	(55.1)
	Skin	56	(10.1)	65	(11.9)	121	(11.0)
	Lung	279	(50.4)	280	(51.1)	559	(50.7)
	Liver	247	(44.6)	271	(49.5)	518	(47.0)
	Spleen	2	(0.4)	2	(0.4)	4	(0.4)
	Lymph Nodes	268	(48.4)	274	(50.0)	542	(49.2)
	Esophagus	1	(0.2)	0		1	(0.1)
	Stomach	2	(0.4)	0		2	(0.2)
	Breast	113	(20.4)	104	(19.0)	217	(19.7)
	Breast only	1	(0.2)	4	(0.7)	5	(0.5)
	Ovary	4	(0.7)	10	(1.8)	14	(1.3)
	Pancreas	1	(0.2)	2	(0.4)	3	(0.3)
	Colon/Rectum	2	(0.4)	0		2	(0.2)
	Adrenal Gland	10	(1.8)	15	(2.7)	25	(2.3)
	Uterus	1	(0.2)	0		1	(0.1)
	Kidney	4	(0.7)	5	(0.9)	9	(0.8)
	Bladder	0		1	(0.2)	1	(0.1)
	Larynx	1	(0.2)	1	(0.2)	2	(0.2)
	Thyroid Gland	1	(0.2)	2	(0.4)	3	(0.3)
	Gallbladder	0		1	(0.2)	1	(0.1)
	Bile Ducts	0		1	(0.2)	1	(0.1)
	Ureter	0		1	(0.2)	1	(0.1)
	Extremeties	1	(0.2)	2	(0.4)	3	(0.3)
	Chest Wall	57	(10.3)	57	(10.4)	114	(10.3)
Number of Organs Involved	1	113	(20.4)	92	(16.8)	205	(18.6)
	2	174	(31.4)	177	(32.3)	351	(31.9)
	3	153	(27.6)	149	(27.2)	302	(27.4)
	4	80	(14.4)	80	(14.6)	160	(14.5)
	5	25	(4.5)	31	(5.7)	56	(5.1)
	>=6	9	(1.6)	18	(3.3)	27	(2.5)
	Missing	0		1	(0.2)	1	(0.1)

Source: Study 301 CSR, Table 14.1.5.2

Prior therapy

Table 14. History of previous anticancer treatment (ITT population)

Parameter	Treatment Groups		Total (N=1102)
	E7389 (N=554)	Capecitabine (N=548)	
Number of previous chemotherapy regimens, n (%)			
0	1 (0.2)	0	1 (0.1)
1	147 (26.5)	153 (27.9)	300 (27.2)
2	319 (57.6)	314 (57.3)	633 (57.4)
3	84 (15.2)	78 (14.2)	162 (14.7)
4	3 (0.5)	2 (0.4)	5 (0.5)
5	0	1 (0.2)	1 (0.1)
Duration of last chemotherapy (months)			
N	553	546	1099
Mean (SD)	3.7 (3.19)	3.7 (3.20)	3.7 (3.19)
Median	3.1	3.1	3.1
Min, Max	0.0, 27.6	0.0, 30.0	0.0, 30.0
Time from last chemotherapy to first dose of study drug (months)			
N	544	545	1089
Mean (SD)	8.6 (14.34)	6.9 (12.26)	7.7 (13.36)
Median	3.8	3.1	3.4
Min, Max	0, 103	0, 163	0, 163
Time to progression after last chemotherapy, n (%)			
≤ 6 months	414 (74.7)	421 (76.8)	835 (75.8)
> 6 months	139 (25.1)	127 (23.2)	266 (24.1)
Number of prior hormonal therapies, n (%)			
0	325 (58.7)	306 (55.8)	631 (57.3)
1	108 (19.5)	123 (22.4)	231 (21.0)
2	60 (10.8)	74 (13.5)	134 (12.2)
3	41 (7.4)	31 (5.7)	72 (6.5)
4	17 (3.1)	9 (1.6)	26 (2.4)
5	2 (0.4)	5 (0.9)	7 (0.6)
≥ 6	1 (0.2)	0	1 (0.1)
Number of prior radiotherapy courses n (%)			
0	141 (25.5)	164 (29.9)	305 (27.7)
1	112 (20.2)	111 (20.3)	223 (20.2)
2	131 (23.6)	134 (24.5)	265 (24.0)
3	90 (16.2)	78 (14.2)	168 (15.2)
4	64 (11.6)	46 (8.4)	110 (10.0)
5	11 (2.0)	7 (1.3)	18 (1.6)

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Parameter	Treatment Groups		Total
	E7389 (N=554)	Capecitabine (N=548)	(N=1102)
≥ 6	5 (0.9)	8 (1.5)	13 (1.2)
Number of prior neo-adjuvant regimens, n (%)[a]			
0	352 (63.5)	361 (65.9)	713 (64.7)
1	190 (34.3)	183 (33.4)	373 (33.8)
2	11 (2.0)	4 (0.7)	15 (1.4)
3	1 (0.2)	0	1 (0.1)
Number of prior adjuvant regimens, n (%)			
0	326 (58.8)	315 (57.5)	641 (58.2)
1	222 (40.1)	230 (42.0)	452 (41.0)
2	6 (1.1)	3 (0.5)	9 (0.8)
Number of prior regimens for locally advanced or metastatic disease, n (%)			
0	116 (20.9)	104 (19.0)	220 (20.0)
1	280 (50.5)	293 (53.5)	573 (52.0)
2	154 (27.8)	146 (26.6)	300 (27.2)
> 2	4 (0.7)	5 (0.9)	9 (0.8)
Number of subjects refractory to taxane and anthracycline, n (%)			
Taxane	250 (45.1)	260 (47.4)	510 (46.3)
Anthracycline	134 (24.2)	139 (25.4)	273 (24.8)
Taxane and Anthracycline	91 (16.4)	103 (18.8)	194 (17.6)
Prior surgical treatment and procedures for conditions under study, n (%)			
Yes	554 (100.0)	548 (100.0)	1102 (100.0)

Note: Refractory is defined as disease progression within 60 days after administration of the last dose of a taxane or anthracyclines. Not all subjects had both a baseline and study termination value for duration of last chemotherapy or time from last chemotherapy to first dose of study drug and are therefore not included in the total number of subjects for those parameters.

ITT = intent-to-treat, Min = minimum, Max = maximum, SD = standard deviation.

a: Includes prior neo-adjuvant, adjuvant, and metastatic disease regimens.

Source: Study 301 CSR, Table 12.

Prior anti-HER2 therapy

Table 15. Prior trastuzumab therapy overall and by number of HER2 positive patients

Disease setting for trastuzumab therapy	Eribulin (n=554)	Capecitabine (n=548)	Total (n=1102)
Neoadjuvant	1 (0.2%)	1 (0.2%)	2 (0.2%)
Adjuvant	12 (2.2%)	13 (2.4%)	25 (2.3%)
Locally advanced/ metastatic	45 (8.1%)	35 (6.4%)	80 (7.3%)
Sum	58 (10.5%)	49 (8.9%)	107 (9.7%)
Proportion of HER2 positive	58/86 (67.4%)	49/83 (59.0%)	107/169 (63.3%)

Source: Study 301 CSR, Tables 14.1.5.3, 14.1.5.4.2, 14.1.5.4.3, and 14.1.5.4.4.

Concomitant Medications

Table 16. Concomitant Medications Used by >10% of Subjects in Either Treatment

Anatomical Class WHO Drug Name (Preferred Term)	Treatment Groups E7389 (N=544) n (%)	Treatment Groups Capecitabine (N=546) n (%)	Total (N=1090) n (%)
Subjects who took at least one medication	496 (91.2)	483 (88.5)	979 (89.8)
Analgesics	**293 (53.9)**	**253 (46.3)**	**546 (50.1)**
Metamizole sodium	56 (10.3)	48 (8.8)	104 (9.5)
Paracetamol	148 (27.2)	112 (20.5)	260 (23.9)
Tramadol	53 (9.7)	64 (11.7)	117 (10.7)
Antiemetics and antinauseants	**170 (31.3)**	**72 (13.2)**	**242 (22.2)**
Ondansetron	132 (24.3)	46 (8.4)	178 (16.3)
Antiinflammatory and antirheumatic products	**209 (38.4)**	**200 (36.6)**	**409 (37.5)**
Ibuprofen	80 (14.7)	74 (13.6)	154 (14.1)
Antineoplastic agents	**186 (34.2)**	**160 (29.3)**	**346 (31.7)**
Capecitabine[a]	112 (20.6)	32 (5.9)	144 (13.2)
Corticosteroids for systemic use	**188 (34.6)**	**112 (20.5)**	**300 (27.5)**
Dexamethasone	128 (23.5)	71 (13.0)	199 (18.3)
Drugs for acid related disorders	**124 (22.8)**	**152 (27.8)**	**276 (25.3)**
Omeprazole	66 (12.1)	85 (15.6)	151 (13.9)
Drugs for functional gastrointestinal disorders	**119 (21.9)**	**132 (24.2)**	**251 (23.0)**
Metoclopramide	49 (9.0)	67 (12.3)	116 (10.6)
Drugs for the treatment of bone diseases	**127 (23.3)**	**118 (21.6)**	**245 (22.5)**
Zoledronic acid	64 (11.8)	74 (13.6)	138 (12.7)
Immunostimulants	**84 (15.4)**	**20 (3.7)**	**104 (9.5)**
Filgrastim	59 (10.8)	16 (2.9)	75 (6.9)

Note: Subjects with two or more medications within a class level and drug name are counted only once within that class level and drug name. Concomitant medications include medications that either (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the first dose of study drug up to 30 days after the last dose of study drug.
WHO = World Health Organization Drug Dictionary version 10.1.
a: Subjects who experienced disease progression were administered capecitabine as a poststudy chemotherapy, after study dug was stopped. If capecitabine was started within 30 days of last dose, it is shown here.

Source: Study 301 CSR, Table 14.

Because concomitant medications were reported until 30 days after the last dose of study drug, capecitabine is listed as a concomitant medication for 144 subjects. However, these subjects experienced disease progression during the study and discontinued study drug before post-progression administration capecitabine was started. These appear under concomitant medications due to the definition in the protocol but in fact, represent post-progression chemotherapy.

Numbers analysed

Table 17. Analysis Sets: All Randomized Subjects

Analysis Set	Treatment Group		
	E7389 (N=554) n (%)	Capecitabine (N=548) n (%)	Total (N=1102) n (%)
Intent-to-Treat	554 (100.0)	548 (100.0)	1102 (100.0)
Per Protocol Set	521 (94.0)	507 (92.5)	1028 (93.3)
Safety Set	544 (98.2)	546 (99.6)	1090 (98.9)
PK Analysis Set	175 (31.6)	NA	175 (15.9%)

NA = not applicable, PK = pharmacokinetic.

Source: Study 301 CSR, Table 9.

Definitions of Analysis Sets:

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

Per Protocol (PP) Population: The Per Protocol population consists of subjects who were randomized and received study drug for at least one full cycle and had no major protocol violations. This analysis population was used for exploratory analyses for all efficacy endpoints.

Safety Population: The Safety population consists of all subjects who received at least one dose of study treatment.

Analyses of the primary and secondary efficacy endpoints were performed on the ITT and PP populations. Safety analyses were performed only on the Safety population.

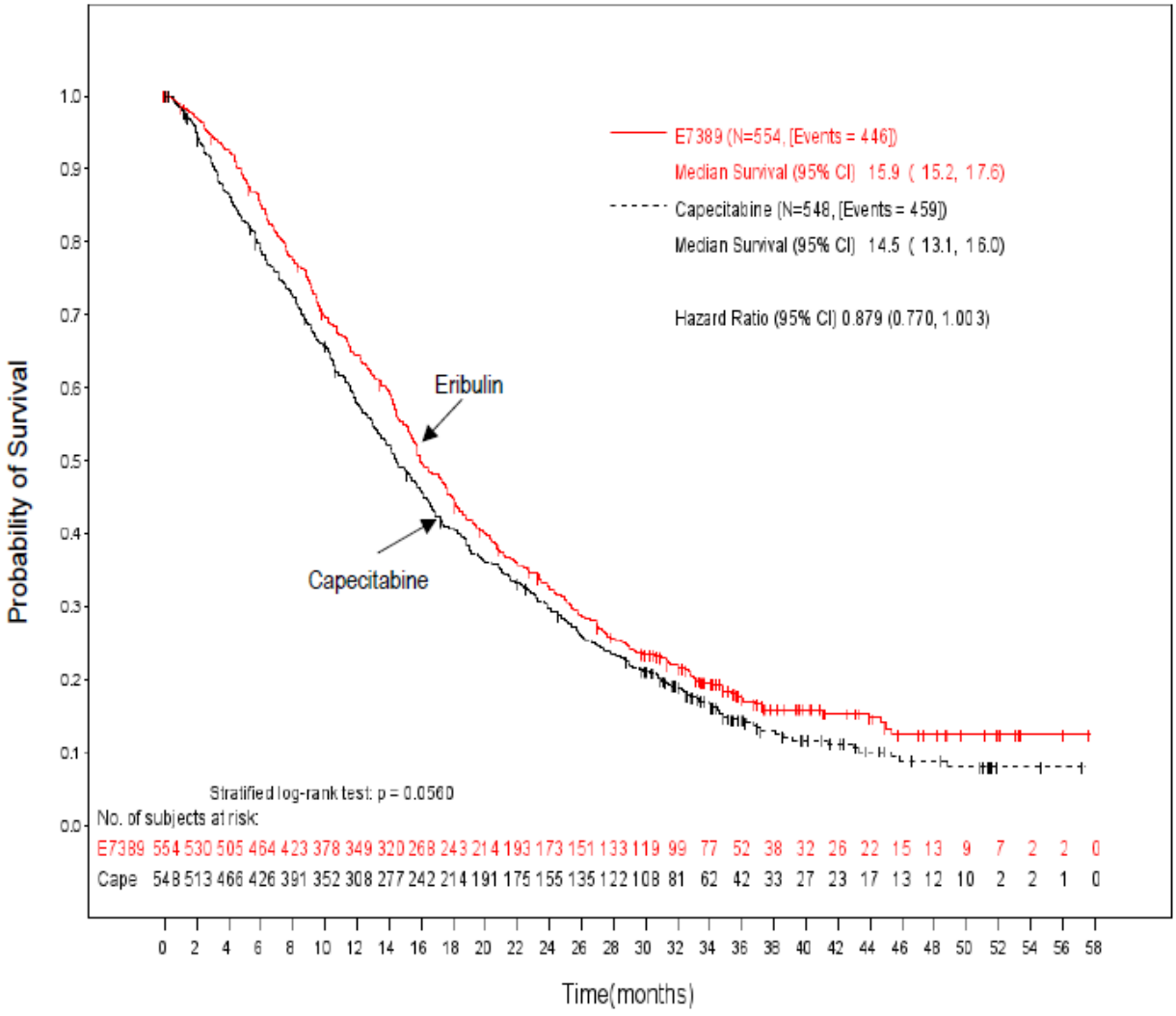
Outcomes and estimation

Primary endpoint – Overall survival (OS)

Table 18. Overall survival, Study 301 (ITT population)

	Treatment Groups	
	Eribulin (N=554) n (%)	**Capecitabine (N=548) n (%)**
Number of subjects who died	446 (80.5)	459 (83.8)
Number of subjects censored before data cut off [a]	21 (3.8)	24 (4.4)
Number of subjects censored at data cut off	87 (15.7)	65 (11.9)
Overall survival, months		
Median (95% CI)	15.9 (15.2, 17.6)	14.5 (13.1, 16.0)
1st Quartile (95% CI)	8.9 (7.7, 9.6)	7.2 (6.1, 8.3)
3rd Quartile (95% CI)	28.8 (26.0, 32.7)	26.9 (24.7, 29.8)
Stratified [b] log-rank test		
P value	0.0560	
Unstratified log-rank test		
P value	0.0439	
Hazard ratio (eribulin/capecitabine) [c]		
Estimate	0.879	
95% CI	(0.770, 1.003)	
Overall survival rate [d]		
1-year (95% CI)	0.644 (0.604, 0.684)	0.580 (0.538, 0.622)
	P = 0.0351	
2-year (95% CI)	0.328 (0.289, 0.368)	0.298 (0.259, 0.337)
	P = 0.3235	
3-year (95% CI)	0.178 (0.144, 0.212)	0.145 (0.113, 0.177)
	P = 0.1751	

CI = confidence interval, HER2 = human epidermal growth factor receptor 2.
a: Subjects censored before database cut off includes subjects who were lost to follow up or withdrew consent.
b: Stratified by HER2 status (clinical database) and geographic region.
c: Hazard ratio was based on a Cox regression model including treatment group as covariate and stratified by HER2 status (clinical database) and geographical region.
d: Overall survival rate at 1, 2, and 3 years and the 95% CI were calculated using Kaplan–Meier estimates and the Greenwood formula. P value was calculated using the generalized Pearson Chi-square test.
Source: Study 301 CSR, Table 15 / SCE, Table 9.



Cape = capecitabine, CI = confidence interval, E7389 = eribulin.
Source: SCE, Figure 1. / Study 301 CSR, Figure 1.
Figure 4. Kaplan–Meier Plot of Overall Survival for the Intent-to-treat Population in Study 301

Adjusted OS (ITT) analysis:

An additional analysis was performed adjusted for number of prior chemotherapy regimens for locally advanced of metastatic disease (0 / ≥ 1) and time to progression after last chemotherapy (≤ 6 months / >6 months). The resulting HR was 0.897 (95% CI: 0.786, 1.024).

PP population

The difference between study arms was smaller in the per protocol population, but still numerically better for eribulin compared with capecitabine, HR: 0.91 (95% CI: 0.794, 1.045). Difference in median OS: 28 days, p= 0.2. Adjusted analysis (as for ITT above), HR: 0.93 (0.809, 1.065).

Primary endpoint – Progression-free survival (PFS)

Table 19. Progression-free survival, Study 301 (ITT population)

	Treatment Group			
	Independent Review		Investigator Review	
PFS Events	E7389 (N=554) n (%)	Capecitabine (N=548) n (%)	E7389 (N=554) n (%)	Capecitabine (N=548) n (%)
Progressive Disease	347 (62.6)	316 (57.7)	418 (75.5)	414 (75.5)
Clinical Progression	NA	NA	25 (4.5)	24 (4.4)
Death	38 (6.9)	44 (8.0)	27 (4.9)	30 (5.5)
Number of subjects censored	169 (30.5)	188 (34.3)	84 (15.2)	80 (14.6)
PFS, days				
Median (95% CI)	126 (106, 131)	129 (120, 147)	127 (120, 131)	126 (113, 136)
1st Quartile (95%)	59 (47, 80)	49 (43, 59)	79 (64, 83)	51 (44, 64)
3rd Quartile (95%)	250 (214, 288)	290 (233, 340)	243 (206, 265)	229 (212, 252)
PFS, months				
Median (95% CI)	4.1 (3.5, 4.3)	4.2 (3.9, 4.8)	4.2 (3.9, 4.3)	4.1 (3.7, 4.5)
1st Quartile (95%)	1.9 (1.5, 2.6)	1.6 (1.4, 1.9)	2.6 (2.1, 2.7)	1.7 (1.4, 2.1)
3rd Quartile (95%)	8.2 (7.0, 9.5)	9.5 (7.7, 11.2)	8.0 (6.8, 8.7)	7.5 (7.0, 8.3)
Stratified log-rank test				
P value	0.3045		0.7361	
Hazard ratio (E7389/capecitabine)				
Estimate	1.079		0.977	
95% CI	0.932, 1.250		0.857, 1.114	
PFS				
6 months				
PFS rate (proportion)	0.357	0.353	0.329	0.350
95% CI	0.311, 0.402	0.306, 0.399	0.288, 0.371	0.308, 0.392
12 months				
PFS rate (proportion)	0.153	0.186	0.128	0.140
95% CI	0.115, 0.191	0.143, 0.228	0.097, 0.158	0.109, 0.172

CI = confidence interval, ITT = intent-to-treat, PFS = progression-free survival.

Source: Study 301 CSR, Table 16.

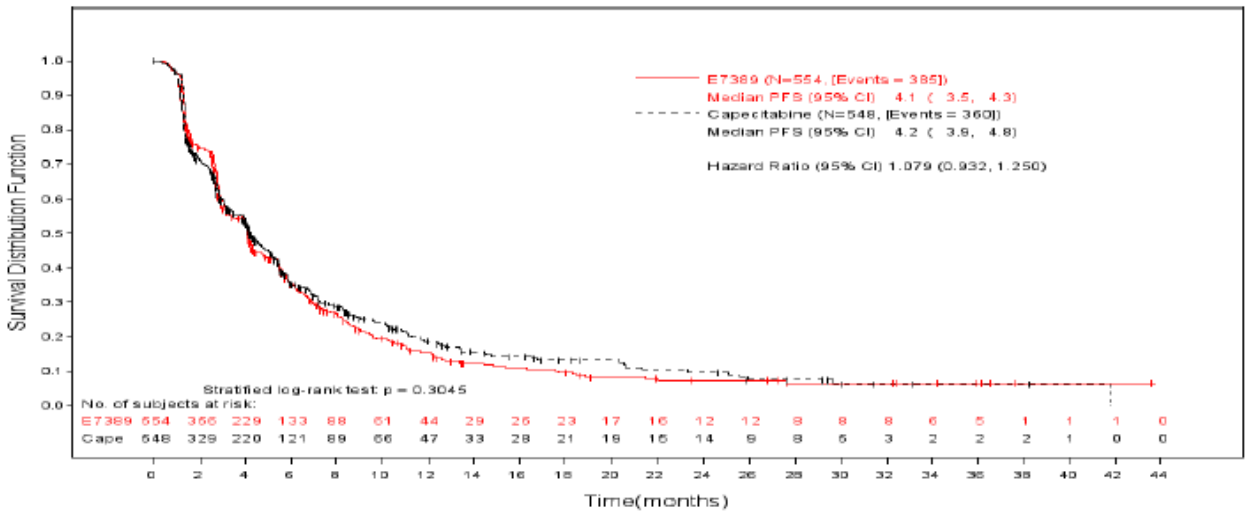


Figure 5. Kaplan–Meier Plot of Progression-free Survival: Independent Review

Source: Study 301 CSR, Figure 2.

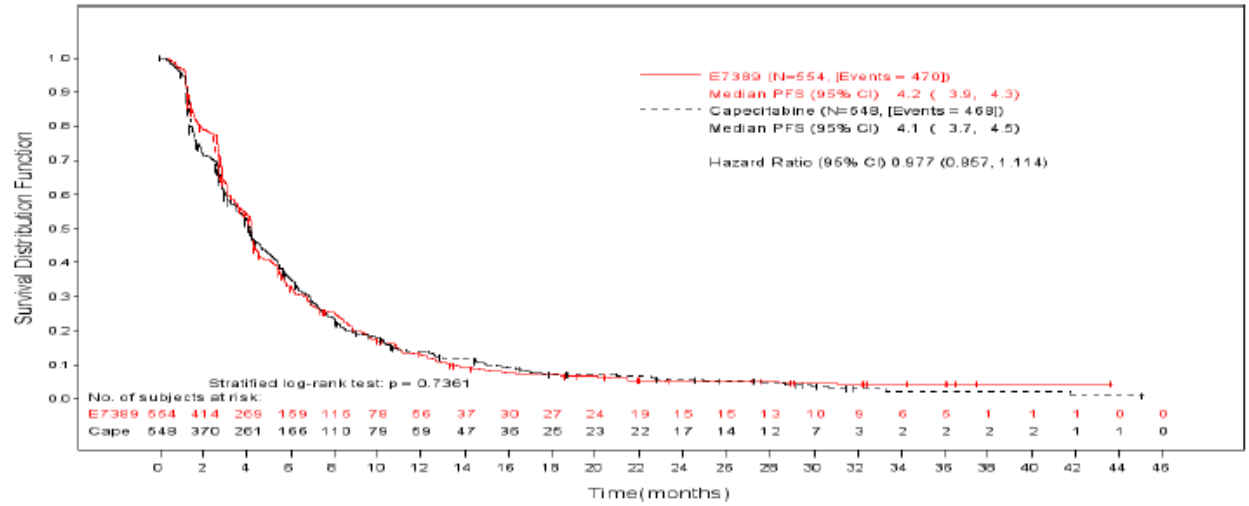


Figure 6. Kaplan–Meier Plot of Progression-free Survival: Investigator Assessment

Source: Study 301 CSR, Figure 3.

Secondary endpoint – Objective response rate (ORR)

Table 20. Best Overall Tumour Response (ITT analysis set)

Parameter	Treatment Group			
	Independent Review		Investigator Review	
	E7389 (N=554) n (%)	Capecitabine (N=548) n (%)	E7389 (N=554) n (%)	Capecitabine (N=548) n (%)
CR	1 (0.2)	0	4 (0.7)	10 (1.8)
PR	60 (10.8)	63 (11.5)	85 (15.3)	99 (18.1)
SD	313 (56.5)	303 (55.3)	332 (59.9)	278 (50.7)
PD	125 (22.6)	133 (24.3)	99 (17.9)	126 (23.0)
Not evaluable	11 (2.0)	6 (1.1)	34 (6.1)	35 (6.4)
Unknown [a]	44 (7.9)	43 (7.8)	0	0
Objective response rate (CR + PR)	61 (11.0)	63 (11.5)	89 (16.1)	109 (19.9)
95% CI [b]	8.5, 13.9	8.9, 14.5	13.1, 19.4	16.6, 23.5
P value	0.849		0.100	
Clinical benefit rate [c]				
(CR+PR+SD≥6 months)	145 (26.2)	147 (26.8)	182 (32.9)	188 (34.3)
95% CI [b]	22.6, 30.0	23.2, 30.7	29.0, 36.9	30.3, 38.4
P value	0.838		0.611	
Unconfirmed PR/CR due to protocol specifications [d]			21 (3.8)	16 (2.9)

CI = confidence interval, CR = complete response, ITT = intent-to-treat, PD = progressive disease, PR = partial response, SD = stable disease.
a: Subjects with "unknown," including those who had no Baseline scans or who had only Baseline scans.
b: Exact Clopper–Pearson 2-sided confidence interval.
c: For clinical benefit, SD must be at least 6 months.
d: Unconfirmed due to confirmatory bone scan not performed.

Source: Study 301 CSR, Table 17.

In the PP population the ORR based on Independent review was 11.5% and 12.2% in the eribulin and capecitabine arms, respectively (p= 0.8); the clinical benefit rate (CBR) was 27.4% and 28.6% (p= 0.7), respectively. For investigator assessments the ORRs were 17.1% and 21.1% (p= 0.1), and CBR 34.2% and 36.3% (p= 0.6) for eribulin and capecitabine arms, respectively.

Secondary endpoint – Duration of response (DoR)

Table 21. Duration of Response for Complete Responses and Partial Responses (ITT set)

Parameter	Treatment Group			
	Independent Review		Investigator Review	
	E7389 (N=554) n (%)	Capecitabine (N=548) n (%)	E7389 (N=554) n (%)	Capecitabine (N=548) n (%)
Number of subjects				
Responders	61 (11.0)	63 (11.5)	89 (16.1)	109 (19.9)
Nonresponders	487 (87.9)	481 (87.8)	465 (83.9)	438 (79.9)
No baseline scans	6 (1.1)	4 (0.7)	0	1 (0.2)
Subjects with confirmed response	**61 (100.0)**	**63 (100.0)**	**89 (100.0)**	**109 (100.0)**
CR	1 (1.6)	0	4 (4.5)	10 (9.2)
PR	60 (98.4)	63 (100.0)	85 (95.5)	99 (90.8)
PD or death	44 (72.1)	34 (54.0)	76 (85.4)	86 (78.9)
Censored	17 (27.9)	29 (46.0)	13 (14.6)	23 (21.1)
Duration of response (CR + PR) (days)				
Median	198 (150, 273)	330 (208, 541)	197 (150, 232)	205 (175, 241)
1st Quartile (95% CI)	127 (87, 150)	169 (126, 213)	126 (91, 139)	142 (119, 161)
3rd Quartile (95% CI)	330 (273, 491)	703 (483, 1223)	297 (254, 420)	392 (283, 722)

CI = confidence interval, CR = complete response, ITT = intent-to-treat, PD = progressive disease, PR = partial response.

Source: Study 301 CSR, Table 18.

The MAH considers that the difference in IRC vs. investigator review in the median DoR for the capecitabine group may have been influenced by informative censoring in this relatively small number of subjects. In addition, five subjects in the capecitabine group had particularly long DoR contributing to a 3rd quartile of 703 days (95% CI = 483, 1223) compared with the 3rd quartile for the eribulin group of 330 days (95% CI = 273, 491) as assessed by IRC. Three of these five subjects were ongoing without disease progression at the time of data cut off, one subject had progressive disease assessed by IRC on the same date as the investigator, and one subject withdrew consent prior to IRC review. In addition, responders are not a randomized group and, therefore, direct comparison of duration cannot be made between groups.

Secondary endpoint – Quality of Life

The MAH stated that subjects in the eribulin treatment group had a better QoL in parameters linked to gastrointestinal effects, while subjects in the capecitabine group had a better QoL in parameters related to hair loss. Mean scores for nausea and vomiting at baseline were 10.0 and 10.1, respectively, and improved in the eribulin group by a mean of -1.01 and deteriorated in the capecitabine group by a mean of +2.79. The change from baseline in mean scores for diarrhoea were -0.10 for subjects in the eribulin group (improvement) and +4.46 for subjects in the capecitabine group (deterioration). The change from baseline in mean scores for systemic therapy side effects, which includes 'upset by hair loss,' were +3.71 for subjects in the eribulin group (deterioration) and -1.13 for subjects in the capecitabine group (improvement). Symptoms of hand and foot syndrome were not assessed by the QoL questionnaire. Mean pain scores decreased (improved) in both treatment groups.

According to the Statistical Analysis Plan (SAP) the primary QoL analysis would focus on the global health status/QoL) at week 6:

Table 22. Summary of EORTC QLQ-C30 Scores for Global health status / QoL, by visit

		E7389 (N=554)		Capecitabine (N=548)	
Visit		Actual	Change from Baseline	Actual	Change from Baseline
Baseline	n	526		518	
	Mean	56.3		54.7	
	SD	22.21		21.67	
	Median	50.0		50.0	
	Min	0		0	
	Max	100		100	
6 Weeks	n	446	438	419	406
	Mean	57.2	0.1	57.8	1.7
	SD	20.97	19.23	22.33	20.69
	Median	58.3	0.0	58.3	0.0
	Min	0	-50	0	-83
	Max	100	67	100	67

Source: Study 301 CSR, Table 14.2.9.1.

On average without adjustments for attrition or intrasubject variability, global health status / QoL showed no meaningful improvement or deterioration for eribulin or for capecitabine. (CSR, p. 111)

Table 23. Quality of Life Assessment: Eribulin versus Capecitabine (ITT)

	Average Comparative Incremental Change from Baseline	95% Confidence Intervals	Wald P-value
QLQ-C30 Symptom Scales			
Fatigue	0.26	(-2.08, 2.59)	0.8303
Nausea and vomiting	-1.86	(-3.69, -0.04)	0.0448
Pain	0.97	(-1.61, 3.56)	0.4606
Dyspnoea	0.41	(-2.42, 3.24)	0.7782
Insomnia	1.29	(-1.58, 4.15)	0.3790
Appetite loss	1.23	(-1.57, 4.03)	0.3885
Constipation	-0.24	(-2.66, 2.18)	0.8441
Diarrhoea	-3.81	(-6.02, -1.60)	0.0007
Financial difficulties	-0.40	(-3.57, 2.77)	0.8038
BR23 Functional scales			
Body image	-4.67	(-7.21, -2.13)	0.0003
Sexual functioning	1.01	(-0.74, 2.77)	0.2570
Sexual enjoyment	2.29	(-3.07, 7.65)	0.4022
Future perspective	-1.18	(-4.51, 2.14)	0.4857
BR23 Symptom Scales			
Systemic therapy side effect	5.16	(3.49, 6.83)	<0.0001
Breast symptoms	0.69	(-1.12, 2.50)	0.4549
Arm symptoms	-0.33	(-2.39, 1.73)	0.7542
Upset by hair loss	9.35	(1.34, 17.36)	0.0221

Results for QLQ-C30 symptoms scales and BR23 module based on weighted generalized estimating equations where the weights are predicted probabilities for survival at 12 months with controls for age, race, no. of organs, lines of chemotherapy, HER2/neu status(ICH), ECOG, no. of hormonal therapies, no. of therapies in neoadjuvant setting and visceral disease. An exchangeable correlation matrix was specified.
Positive values favour eribulin in Functional scales and negative values favour eribulin in Symptom scales.
Source: Study 301 CSR, table 14.2.9.9.

Secondary endpoint – Tumour-related symptom assessments (VAS pain scores)

Overall, most subjects reported decreases from Baseline in VAS pain scores during the trial, with similar decreases in each treatment group at each study visit. However, at Study Termination, the mean decreases from Baseline in VAS pain scores for subjects in the eribulin group was 3.7 (n=431 subjects) and current mean pain score 16.3, while subjects in the capecitabine group reported no overall change from Baseline to Study Termination in VAS pain scores: + 0.4 (n=407) with current mean pain score 18.9. The mean pain scores were similar at baseline; 20.9 (n= 532) and 20.6 (n=531) in the eribulin and capecitabine arms, respectively. The VAS results are not independent of the analgesic use.

Secondary endpoint – Consumption of analgesics during the study

The overall analgesic use was 53.9% vs. 46.3% for eribulin and capecitabine, respectively, with paracetamol use at 27.2% and 20.5%, respectively. In a separate analysis, opioid use rates were 40.8% vs.35.9%, respectively.

Secondary endpoint – ECOG performance status

Most subjects in both treatment groups had an Eastern Cooperative Oncology Group Score (ECOG) score of 0 or 1 at baseline and study termination. One subject in the E7389 group and four subjects in the capecitabine group had a shift from 0 at baseline to 3 at study termination and one subject in the capecitabine group had a shift from 0 at baseline to 4 at study termination. Similar results were observed for the PP population.

Table 24. ECOG Performance Status at Termination Visit (ITT Population)

Visit ECOG Performance Status	E7389 (N=554) n	(%)	Capecitabine (N=548) n	(%)
Baseline				
n	554		548	
0	250	(45.1)	230	(42.0)
1	293	(52.9)	301	(54.9)
2	11	(2.0)	16	(2.9)
3	0		1	(0.2)
Study Termination				
n	493		492	
0	187	(37.9)	172	(35.0)
1	235	(47.7)	242	(49.2)
2	55	(11.2)	55	(11.2)
3	15	(3.0)	20	(4.1)
4	1	(0.2)	3	(0.6)

Source Study 301 CSR, Table 14.2.10.1. ECOG = Eastern Cooperative Oncology Group

Ancillary analyses

OS and PFS - adjusted analyses

Oestrogen receptor and triple-negative status are well known prognostic factors for outcome in breast cancer. An imbalance was observed for these two receptors' status between the two treatment groups in Study 301. Therefore, post-hoc OS and PFS analyses adjusted for these factors were performed:

Table 25. OS and PFS - adjusted by disease characteristics

Analysis	OS	PFS - Investigator Assessment	PFS - IRC Assessment
Adjusted by ER Status			
Hazard ratio (95% CI)	0.863 (0.754, 0.988)	0.951 (0.831, 1.087)	1.038 (0.893, 1.207)
P value	0.0331	0.4722	0.6106
Adjusted by PR Status			
Hazard ratio (95% CI)	0.875 (0.764, 1.001)	0.973 (0.850, 1.113)	1.094 (0.940, 1.272)
P value	0.0529	0.6937	0.2375
Adjusted by Triple-negative Status			
Hazard ratio (95% CI)	0.859 (0.752, 0.981)	0.950 (0.832, 1.084)	1.041 (0.898, 1.208)
P value	0.0253	0.4572	0.5843
Adjusted by Hormonal Receptor Status			
Hazard ratio (95% CI)	0.863 (0.754, 0.988)	0.949 (0.829, 1.086)	1.042 (0.896, 1.212)
P value	0.0330	0.4599	0.5798
Adjusted by ER Status and PR Status			
Hazard ratio (95% CI)	0.865 (0.754, 0.993)	0.966 (0.842, 1.110)	1.080 (0.924, 1.261)
P value	0.0393	0.6338	0.3216
Adjusted by ER and Triple-negative Status			
Hazard ratio (95% CI)	0.864 (0.755, 0.990)	0.950 (0.830, 1.087)	1.038 (0.893, 1.208)
P value	0.0350	0.4694	0.6097

Table 26. OS analyses adjusted for patient, disease and pre-treatment characteristics

Overall Survival Adjusted by:	
Number of prior chemotherapy regimens for advanced or metastatic disease: 0, 1, or ≥ 2	
Hazard ratio (95% CI)	0.875 (0.764, 1.001)
P value	0.0526
Time to progression after the last chemotherapy: ≤ 6 months, or > 6 months	
Hazard ratio (95% CI)	0.892 (0.780, 1.020)
P value	0.0943
Age group: < 65 years, or ≥ 65 years	
Hazard ratio (95% CI)	0.877 (0.767, 1.003)
P value	0.0557
Setting of prior chemotherapy *	
Hazard ratio (95% CI)	0.875 (0.766, 1.000)
P value	0.0512
Sites of disease: visceral only, or other	
Hazard ratio (95% CI)	0.852 (0.744, 0.975)
P value	0.0201
Number of organs involved: ≤ 2, or > 2	
Hazard ratio (95% CI)	0.859 (0.750, 0.984)
P value	0.0278

Progression while on treatment with a taxane or other microtubule inhibiting agent: yes, or no	
Hazard ratio (95% CI)	0.877 (0.767, 1.003)
P value	0.0549
Taxane refractory: yes, or no	
Hazard ratio (95% CI)	0.877 (0.767, 1.003)
P value	0.0541

* Anthracyclines and taxanes both received as (neo)adjuvant therapy, or at least one of them received as treatment for metastatic disease.

Hazard ratio was estimated using Cox regression model stratified by geographic region, HER2 status, and the corresponding baseline status. P value is based on stratified log-rank test with the same stratification factors as the Cox regression model. CI = confidence interval.

Post-hoc multi-adjusted OS analysis

At the request of the CHMP, a post-hoc analysis of OS and PFS was performed, adjusted for HER2/neu status (positive/negative/unknown), age (<65 vs. ≥65 years old), visceral disease (yes/no), ECOG performance status (0/≥1), ER status (positive/negative/unknown), PgR status (positive/negative/unknown), triple-negative status (yes/no), tumour grade (1-2 vs. 3-4 vs. missing), number of prior chemotherapy regimens (0-1 vs. ≥2), duration of last prior therapy, time since last prior therapy, time since original diagnosis, and geographic region (North America, Western Europe, Eastern Europe, Latin America, South Africa, Asia). The HR (95%CI) for OS-, PFS-(investigator), and PFS- (IRC)-adjusted analyses are 0.94 (0.82, 1.07), 1.01 (0.89, 1.16), and 1.11 (0.95, 1.28), respectively.

OS subgroup analyses

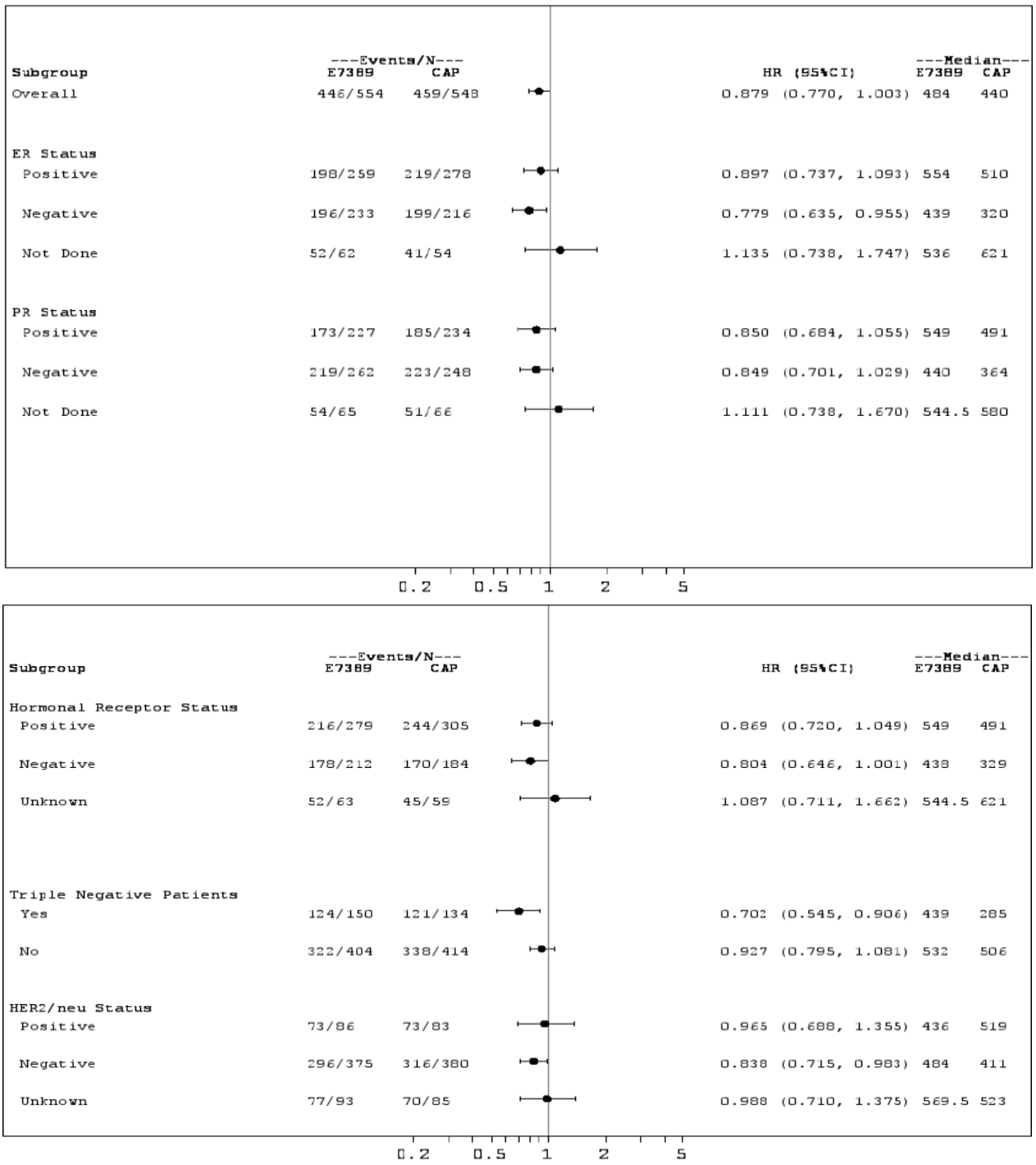
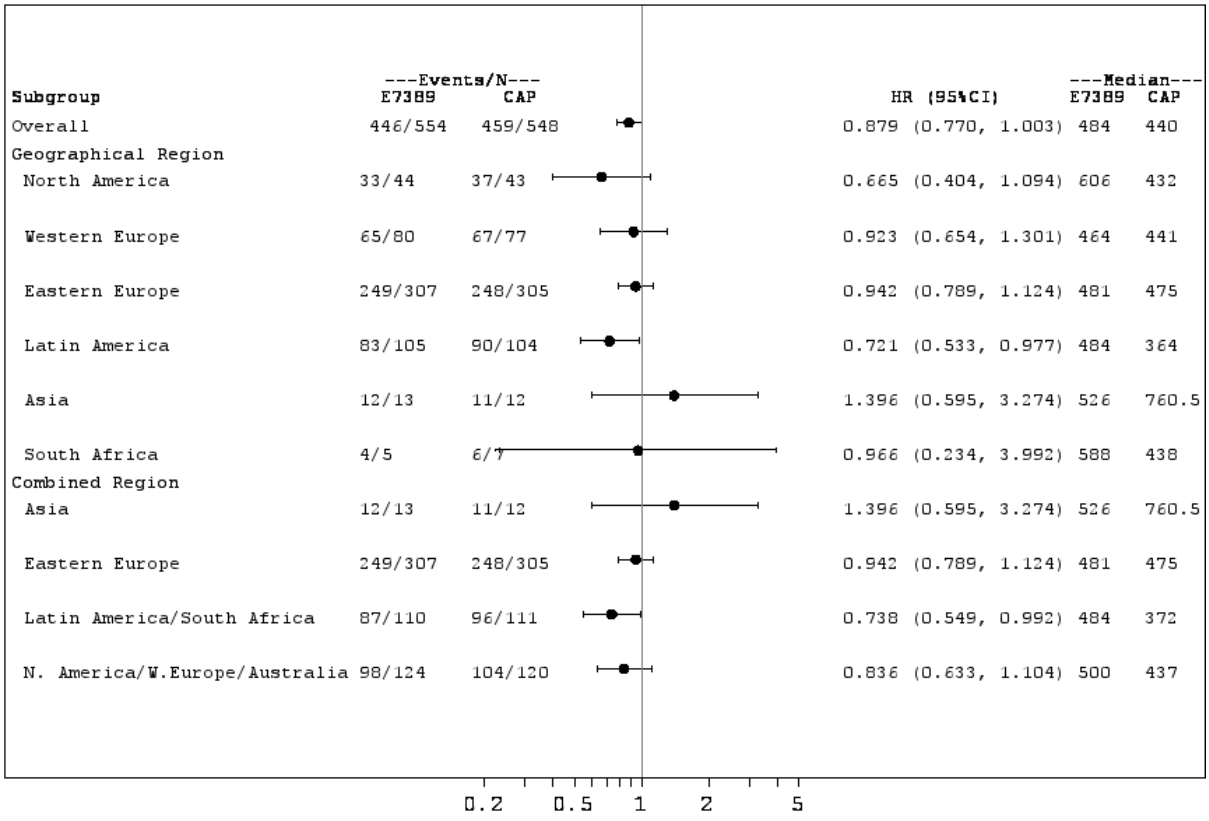


Figure 7. Overall Survival - Hazard Ratios by Receptor Status (ITT Population) Study 301

Source: Study 301 CSR, Figure 14.2.8.2.1



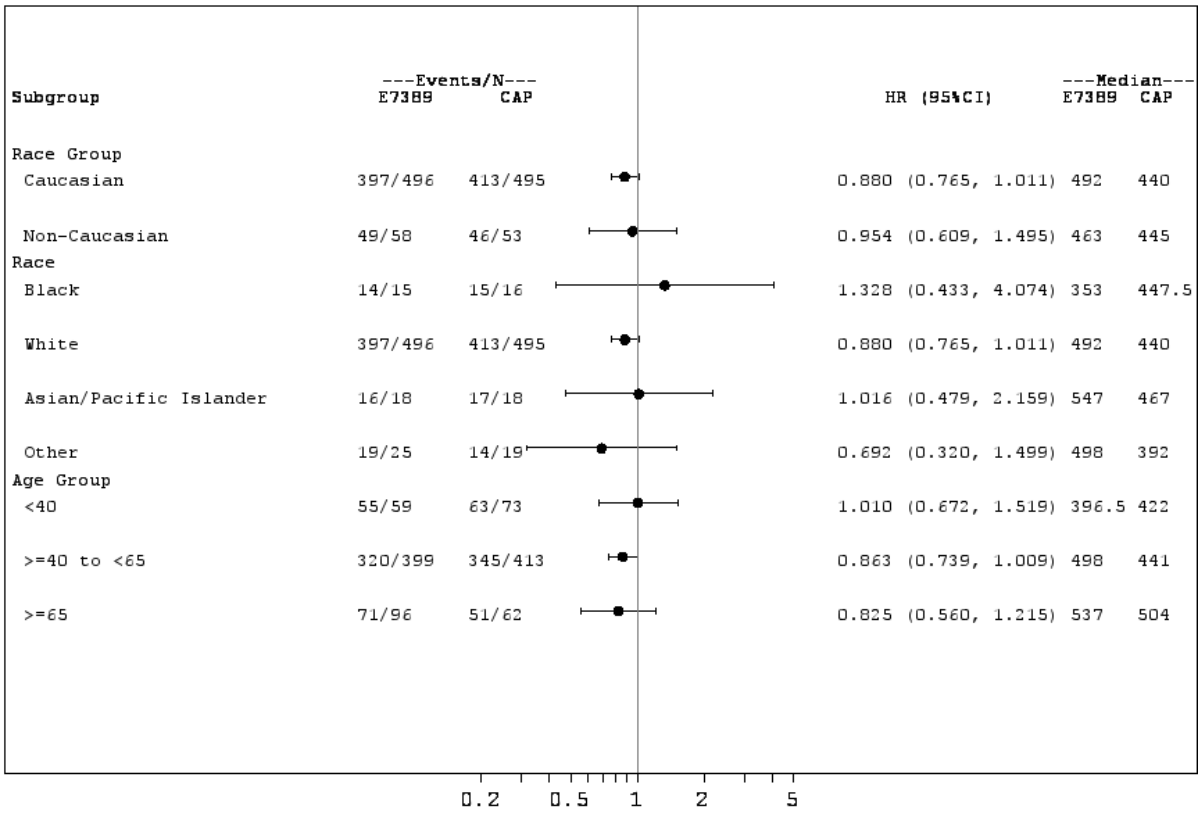


Figure 8. Subgroup Analyses of Overall Survival: Demographics (ITT Population)
Source: Study 301 CSR, Figure 7.

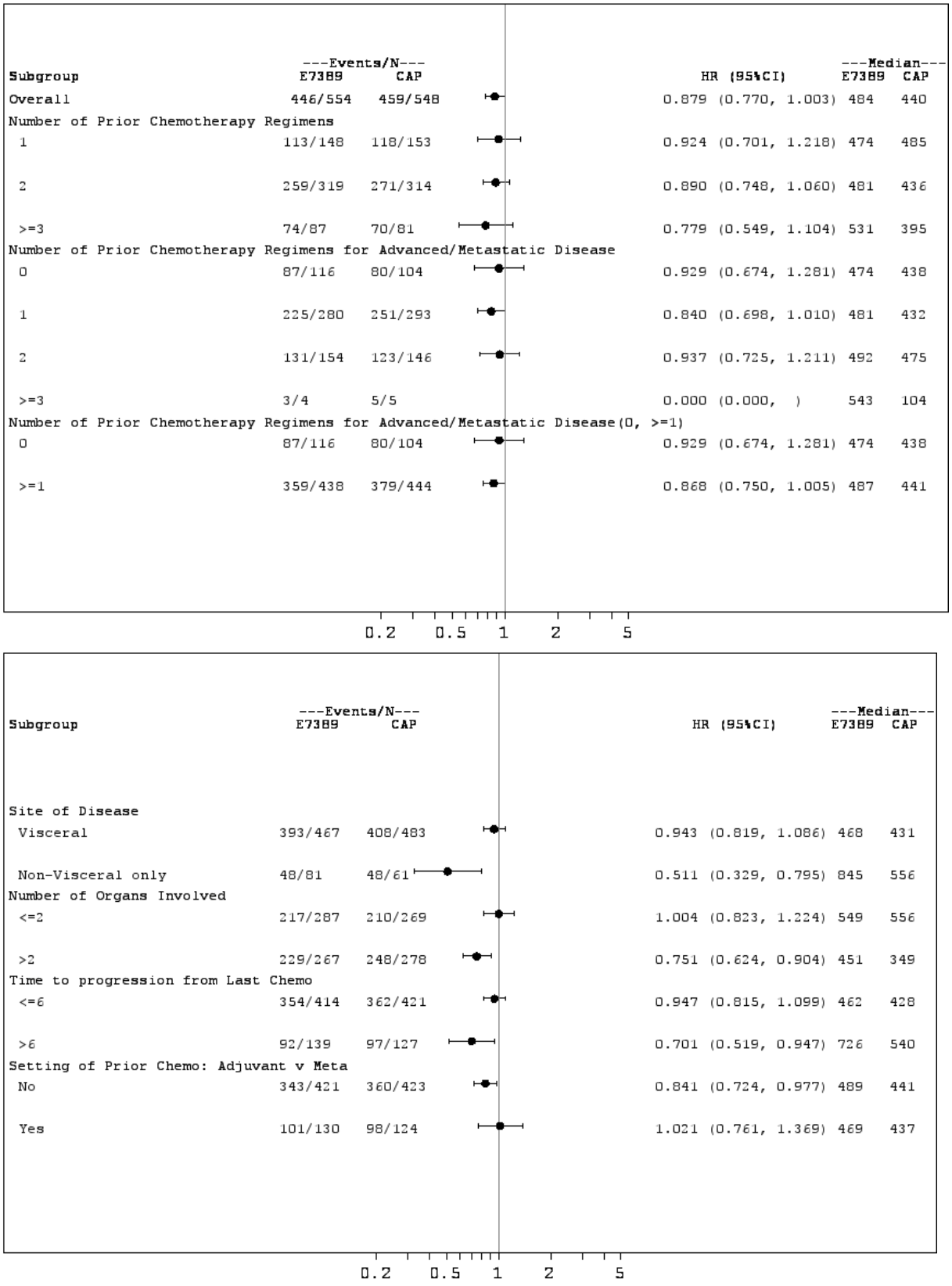


Figure 9.Subgroup Analyses of Overall Survival: Disease Status (ITT Population)
Source: Study 301 CSR, Figure 8.

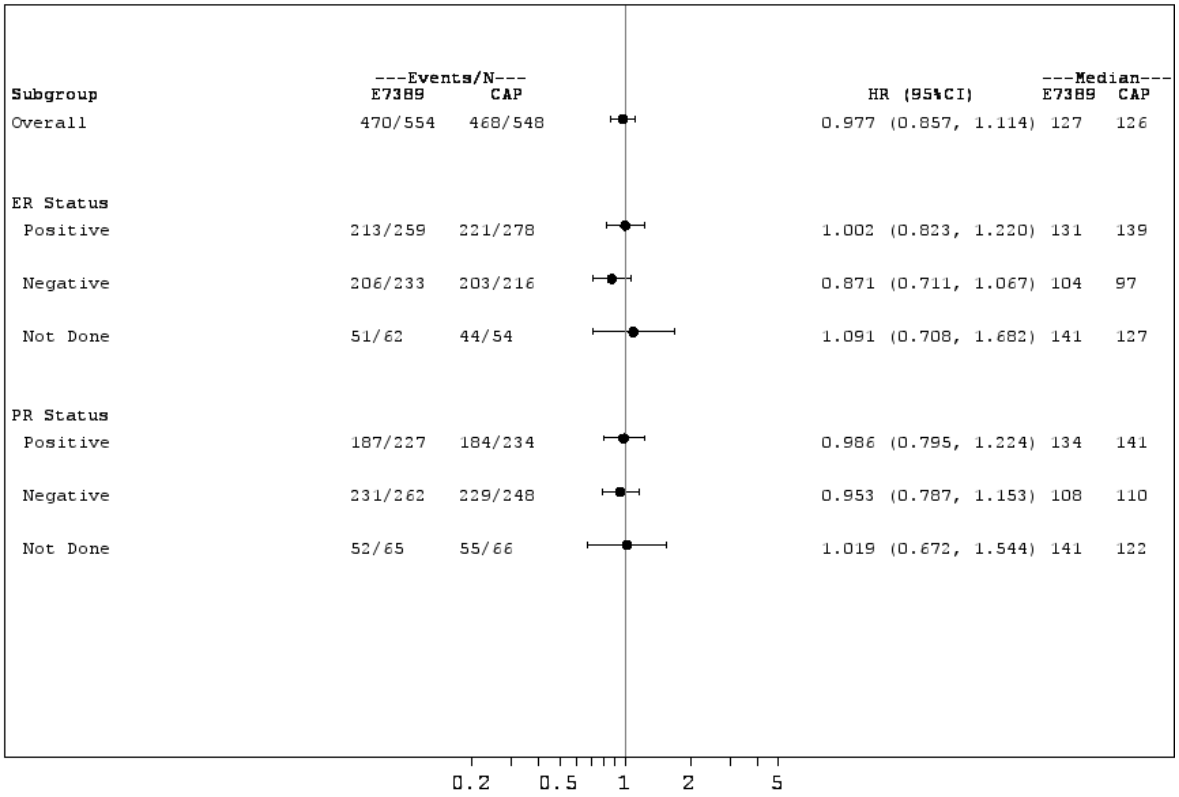
PFS subgroup analyses

The PFS sub-group analyses of receptor status (Figure 10) showed no relevant differences between study arms, except a trend of better outcome for eribulin vs. capecitabine in the triple-negative subgroup; and a trend of better outcome in the capecitabine compared with the eribulin arm in the HER2-positive subgroup.

The PFS sub-group analyses of demographics showed a HR of 1.1 in favour of capecitabine in the Eastern Europe subgroup, which is the largest geographic region subgroup (n=612 of 1102; 56% of ITT) (Figure 11). This is in contrast with the OS subgroup analysis (Figure 7) with a HR of 0.94.

With regard to disease status, patients with non-visceral disease only (n= 142; 13% of the ITT) had a better HR point estimate of 0.83 (almost the only disease characteristic, apart from the receptor statuses, with a PFS HR below 1.0).

It is also noted that the subgroup with 1 prior chemotherapy regimen for advanced disease (sought indication) had a PFS HR consistent with the overall results, i.e. HR 1.029 (95% CI: 0.838, 1.263), and 2 days' difference in median PFS favouring capecitabine.



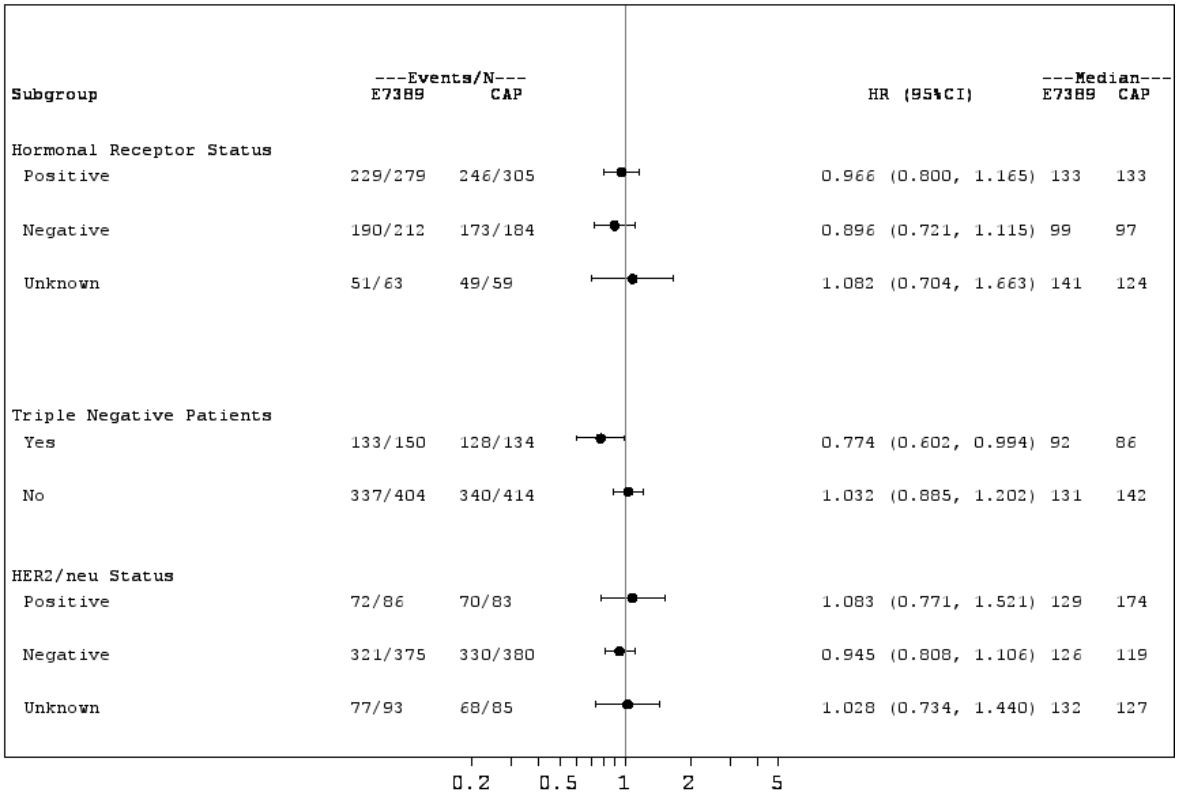
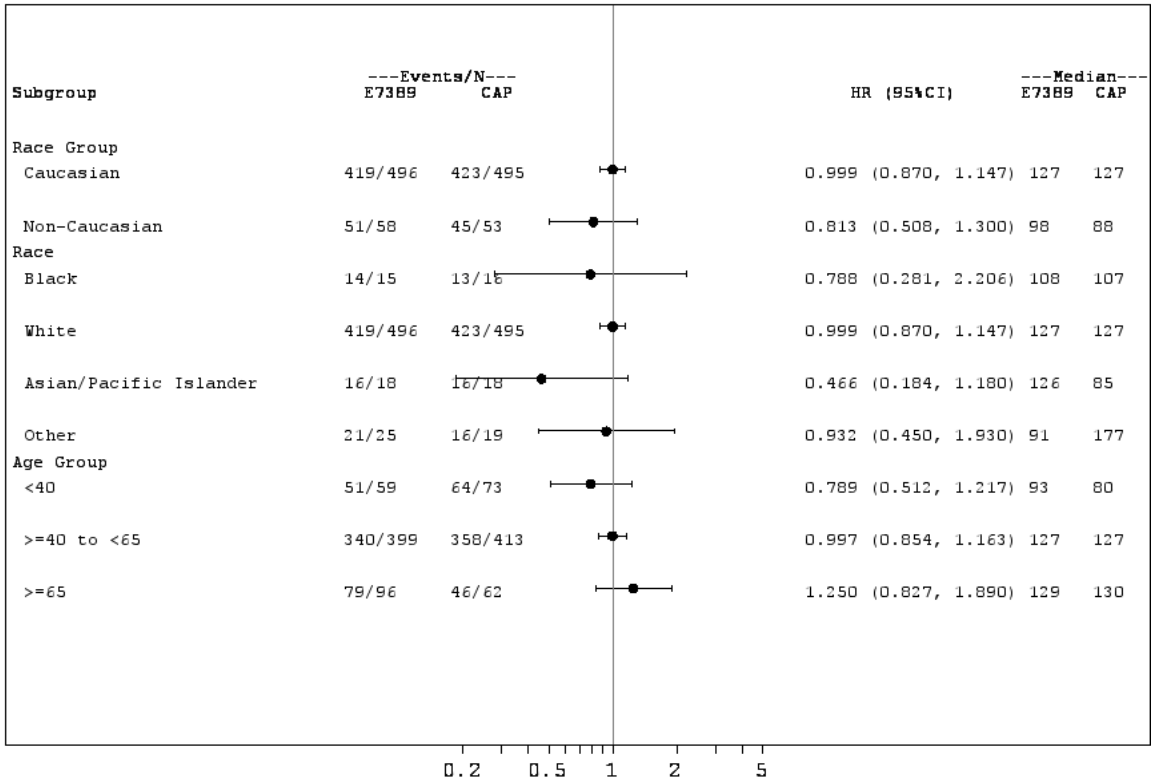


Figure 10. Progression Free Survival - Hazard Ratios by Receptor Status (Investigator assessment, ITT Population, Study 301)

Source: Study 301 CSR, Figure 14.2.8.2.3. (PFS investigator assessment)



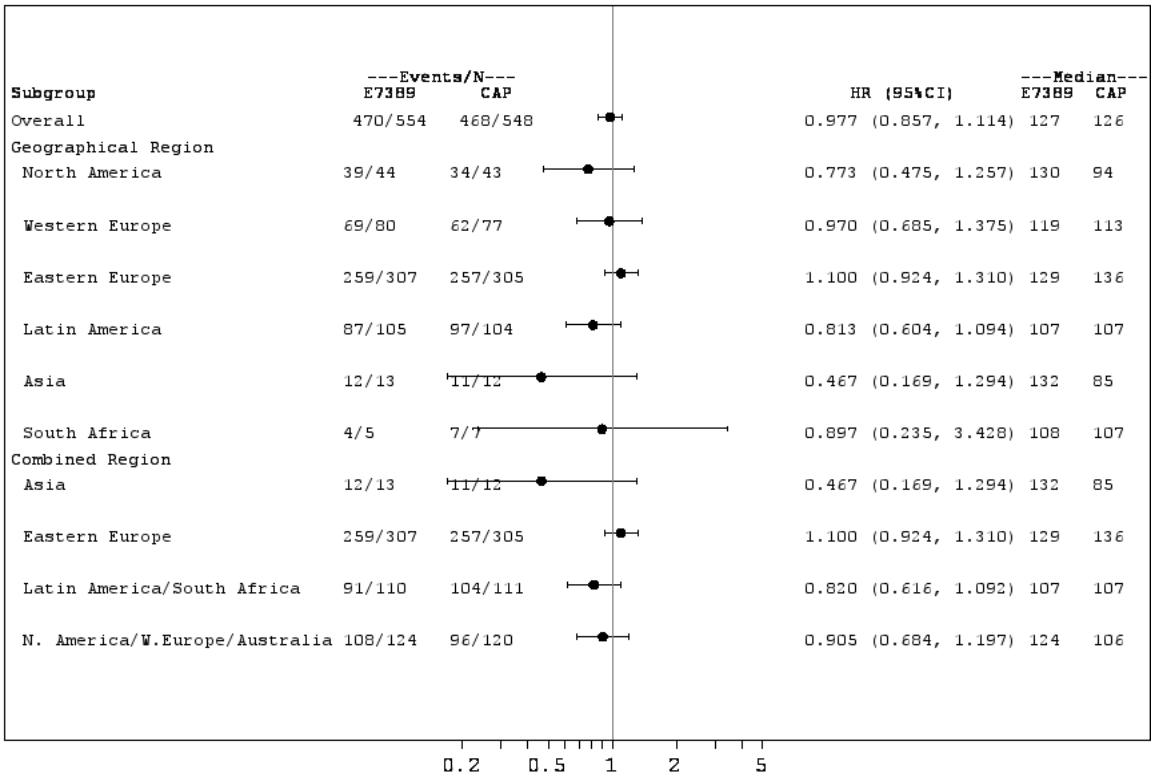
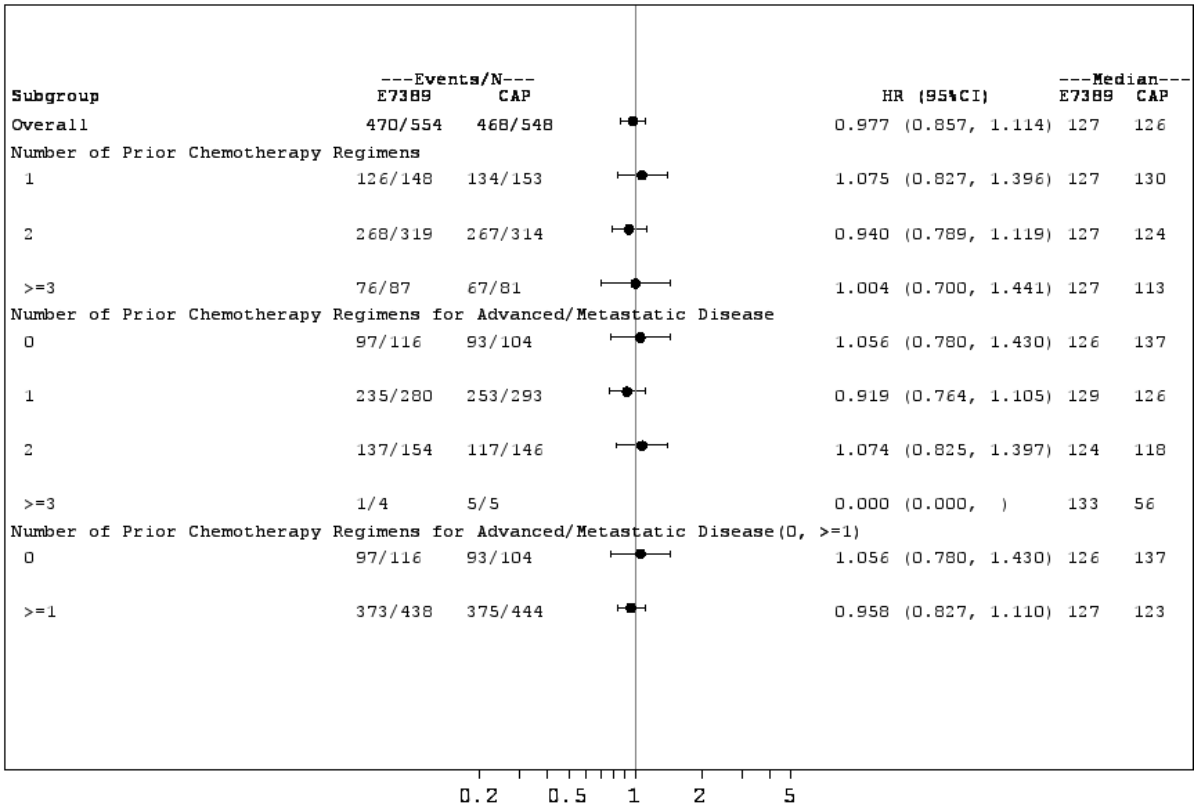


Figure 11. Subgroup Analyses of Progression-free Survival: Demographics (INV, Study 301)

Source: Study 301CSR, Figure 14.2.8.1.3. (PFS investigator assessment)



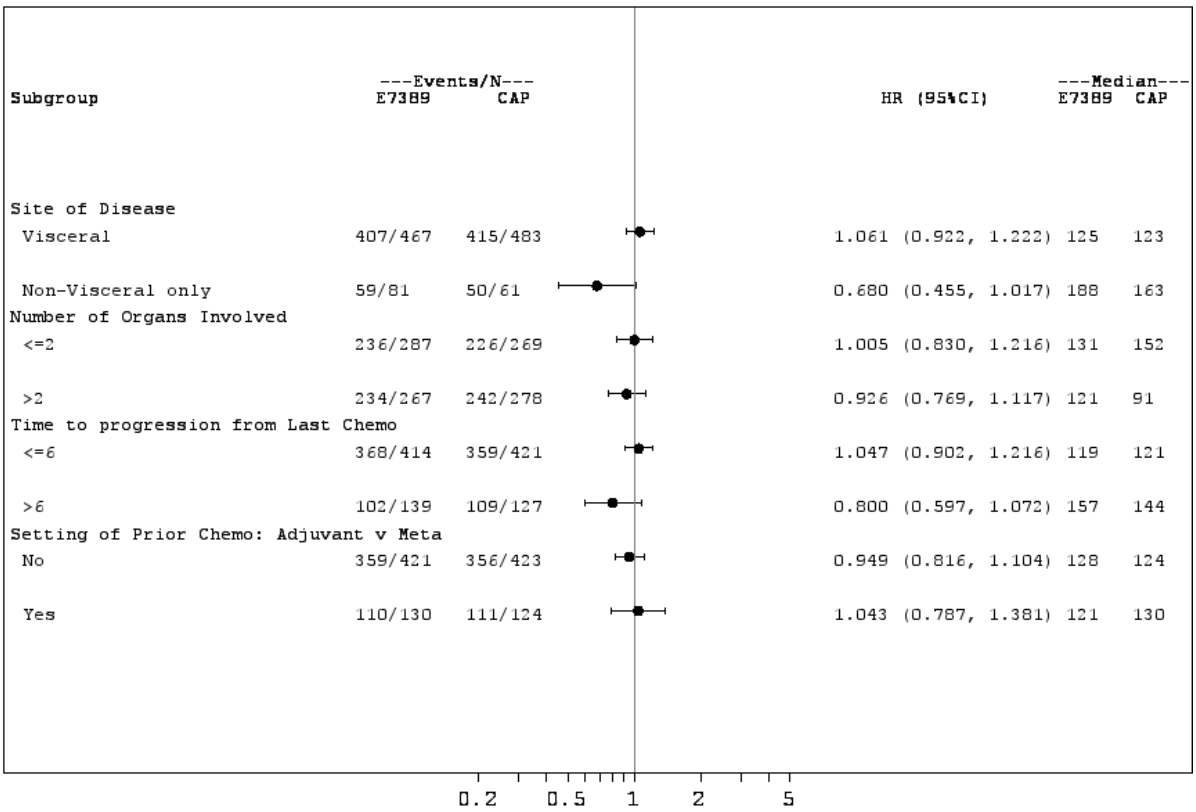


Figure 12. Subgroup Analyses of Progression-free Survival: Disease Status (INV, Study 301)

Source: Study 301CSR. Figure 14.2.8.3.3 (PFS investigator assessment)

HER2 subgroup analyses across studies

Pooled data for the HER2 subgroups of Studies 305 and 301 were provided.

HER2 negative subgroups of Studies 305 and 301:	OS* HR: 0.841 (0.743, 0.952) PFS HR: 0.839 (0.741, 0.949)
HER2 positive subgroups of Studies 305 and 301:	OS* HR: 0.815 (0.624, 1.063) PFS HR: 1.022 (0.780, 1.339)

*: Stratified by geographic region, prior capecitabine use, and Study.

OS – PFS discordance

The discordance between OS and PFS results was identified as a problem with regard to the acceptance of the data, since for a cytotoxic substance a difference in OS would normally be expected to be accompanied by a difference in PFS. Analyses were presented to address this issue, shown below.

PFS events

Table 27. Distribution of PFS events

ITT population	Independent review		Investigator assessment	
	Eribulin (n=554)	Capecitabine (n=548)	Eribulin (n=554)	Capecitabine (n=548)
PFS events, n (%)	385 (69.5)	360 (65.7)	470 (84.8)	468 (85.4)
Death, n (%)	38 (6.9)	44 (8.0)	27 (4.9)	30 (5.5)
Clinical PD, n (%)	N/A	N/A	25 (4.5)	24 (4.4)
PD per RECIST, n (%)	347 (62.6)	316 (57.7)	418 (75.5)	414 (75.5)
New Lesion, n (%)	216 (39.0)	204 (37.2)	271 (48.9)	285 (52.0)
New non-bone lesion, n (%)	202 (36.5)	190 (34.7)	222 (40.1)	235 (42.9)
New bone lesion, n (%)	14 (2.5)	14 (2.6)	49 (8.8)	50 (9.1)
Progression of target lesions, n (%)	92 (16.6)	78 (14.2)	113 (20.4)	92 (16.8)
Progression of non-target lesions, n (%)	39 (7.0)	34 (6.2)	34 (6.1)	37 (6.8)
PFS censored, n (%)	169 (30.5)	188 (34.3)	84 (15.2)	80 (14.6)

Source: Study 301 CSR, Table T_ad_OSPFS_4.1.1 and 4.1.2.

PFS censoring

PFS censoring reasons

Patterns of PFS censoring reasons were analysed. No difference was observed across treatment arms for investigator-based data. However, for independent review, 4% more subjects in the capecitabine group were censored overall (34.4% vs. 30.5%), and 6% more subjects in the capecitabine group had informative censoring (defined as “subjects who had PD/clinical PD in investigator data but PD not observed per IRC”, 26.3% vs. 20.6%).The increase of censoring in the capecitabine group may have resulted in a slight overestimation of PFS according to a simulation study. Further analyses showed consistency in the radiological evaluation of PFS between treatment arms (including analyses of PFS adjusted by baseline characteristics, PFS sensitivity, tumour assessment frequency, and baseline tumour burden, as assessed by the sum of the longest diameter of target lesions, by investigator and independent review).

New anti-cancer therapy was the cause for censoring in 104 (18.8%) of eribulin-treated patients and 112 (20.4%) of capecitabine-treated patients according to IRC /ITT (Table 28).

PFS censoring patterns were overall similar and did not offer an immediate explanation for the different results of the PFS and OS results.

Table 28. Summary of PFS censoring reasons (IRC, ITT)

	E7389 (N=554)	Capecitabine (N=548)
PFS events, n (%)	385 (69.5)	360 (65.7)
PD, n (%)	347 (62.6)	316 (57.7)
Death, n (%)	38 (6.9)	44 (8.0)
PFS censored, n (%)	169 (30.5)	188 (34.3)
PD censored by new anti-cancer, n (%)	1 (0.2)	3 (0.5)
Other therapy, n (%)	1 (0.2)	3 (0.5)
PD censored by missed visits, n (%)	10 (1.8)	12 (2.2)
Death censored by new anti-cancer, n (%)	87 (15.7)	95 (17.3)
Anti-HER2 therapy, n (%)	1 (0.2)	5 (0.9)
Hormonal therapy, n (%)	13 (2.3)	18 (3.3)
Other therapy, n (%)	74 (13.4)	78 (14.2)
Death censored by missed visits, n (%)	11 (2.0)	25 (4.6)
New anti-cancer started without PD or death, n (%)	16 (2.9)	14 (2.6)
Anti-HER2 therapy, n (%)	1 (0.2)	2 (0.4)
Hormonal therapy, n (%)	6 (1.1)	7 (1.3)
Other therapy, n (%)	10 (1.8)	6 (1.1)
No baseline tumor assessment, n (%)	6 (1.1)	4 (0.7)
Other cases without PD or death, n (%)	38 (6.9)	35 (6.4)

Source: Study 301 CSR, Table T_ad_OSPFS_2.1.1

Eastern Europe

The difference (4% overall) in proportion of patients for whom death was censored (due to new anti-cancer treatment or missed visits) was driven by data from Eastern EU sites (with 6.6% difference, Table T_ad_OSPFS_2.2.1). Also in the analysis of informative censoring, the difference in censored deaths is driven by Eastern EU.

EMA sensitivity analysis

A sensitivity analysis was pre-planned according to the EMA guideline on PFS, where PD/death events were NOT censored when they occurred after start of new anticancer treatment or after two or more missed tumour assessments. With HR 1.1 the results do not offer an explanation to the OS-PFS discordance.

Another requested sensitivity analysis where new anticancer therapy was counted as progression indicated no bias by potential differences in the causes for start of new therapy in the PFS analysis.

PFS censoring times

The MAH explored PFS censoring times by IRC and INV in order to investigate if differential censoring times in the eribulin and capecitabine arms could help explain the discordance in OS and PFS results. In the IRC analysis, patients in the capecitabine arm are censored earlier than in the eribulin arm, while time to censoring is the same for INV analysis. This can potentially be due to informative censoring where capecitabine has 6% more informative censoring than the eribulin arm.

When only censored patients are analysed, very similar time to censoring are seen for the two arms for IRC (87 vs. 86 days) and investigator (117 vs. 110 days) assessments. The observed differential pattern of time to censoring along with informative censoring could help explain the PFS results based on IRC analysis; however, given that there is no differential pattern observed for investigator assessment, this does not help to explain the discordance in OS and PFS results in general.

New metastasis

More patients in Study 301 had progression due to enlargement of pre-existing lesions in the eribulin group (27% vs. 24%, eribulin vs. capecitabine, respectively) while more subjects had progression due to new metastasis in the capecitabine group (49% vs. 52%, eribulin vs. capecitabine, respectively).

When all new metastases at any time point during the study, regardless of PFS censoring, where analysed, 5.2%more of the capecitabine-treated patients (57.7%) compared with eribulin-treated patients (52.2%) was observed with a new metastasis during study, according to investigator assessments (Table 29).

The baseline distributions of metastasis sites were overall similar, except for liver metastases which occurred in 5% higher frequency in the capecitabine arm (

Table **12**).

Table 29. Summary of New Metastasis Sites Based on Investigator Assessment for the ITT Population in Study 301

Site of New Metastasis	Eribulin (N=554) n (%)	Capecitabine (N=548) n (%)
Number of subjects with baseline tumor scans	554 (100.0)	547 (99.8)
Number of subjects with any new metastases observed	291 (52.5)	316 (57.7)
New metastasis sites		
CNS (Brain/Spine)	13 (4.5)	25 (7.9)
Lung	59 (20.3)	76 (24.1)
Liver	71 (24.4)	74 (23.4)
Bone	60 (20.6)	62 (19.6)
Skin	23 (7.9)	26 (8.2)
Lymph Nodes	64 (22.0)	55 (17.4)
Breast	12 (4.1)	13 (4.1)
Chest Wall	15 (5.2)	5 (1.6)
Various Parenchymal [a]	3 (1.0)	13 (4.1)
Other [b]	27 (9.3)	39 (12.3)

Note: Percentage for lesion sites is based on number of subjects with any new metastases observed for each group. One subject may have had multiple new metastasis sites.
CNS = central nervous system.
a: Includes spleen, ovary, pancreas, adrenal gland, uterus, kidney, thyroid gland, ureter, and vulva/vagina.
b: Other was an option on the case report form.

Source: SCE, Table 27

The use of INV data is motivated by the presence of 20% informative censoring in the corresponding IRC data. Similar distributions were seen in IRC data (Study 301 CSR, Table T_ad_OSPFS_4.6.4.2.).

Additionally, the MAH observed that subjects who had progression due to a new metastasis were at a higher risk for death (HR=2.12; 95% CI = 1.84, 2.43; P<0.0001) than were those who had progression with no new metastasis. When time to progression by new metastasis (termed "new metastasis-free survival" [nMFS]) was examined as a separate parameter, there was a trend in nMFS in favour of eribulin (HR=0.897 with a median difference of 0.6 months; based on investigator review) compared with the capecitabine arm, and the HR was similar to that of the OS trend. These results could be intuitively expected. However, analyses performed on "new metastasis-free survival" for eribulin vs. capecitabine are "biased" with regard to metastasis sites (capecitabine had more CNS, lung, and "various parenchymal" metastases; eribulin had more lymph node and chest wall sites. These different metastasis sites could be expected to have different prognosis. Furthermore, since the difference in new metastasis as PD between arms was relatively small (5.2% more frequent in the capecitabine arm according to INV; no difference between arms according to IRC) this difference in frequency alone appears unlikely to explain the difference seen in OS. Therefore, these analyses are not further explored. Furthermore, the questions of PD as new metastasis or progression of existing lesion, as well as site of new lesion, are matters of competing risks, why the interpretation of data is complicated.

Similar analyses were undertaken in study 305, a study with more heavily pretreated patients, comparing eribulin with treatment of physicians' choice (2:1 randomisation). In the ITT population, no difference in pattern of progression was observed. In patients assigned to capecitabine prior to randomisation, however, new lesions constituted the first event of progression in 42% vs 36%, eribulin vs. capecitabine, but numbers of patients were small, 77 vs. 45 . With respect to site of metastases, the pattern did not favour the eribulin arm.

Preclinical support

In vitro and in vivo pharmacodynamic studies indicated that eribulin may have additional effects on tumour vascular function and vascular remodelling, migration and invasiveness capacity of cancer cells, and epithelial-mesenchymal transition (EMT)-related pathways, that could offer a plausible mechanistic rationale for a post-progression effect of eribulin compared with capecitabine (

Table **1**).

Effect of post-study therapy

The impact of post study-medication chemotherapy was investigated to determine whether this could account for the trend towards improved survival observed with eribulin (Table 35).

70% of the patients randomised to eribulin received post-study anticancer therapy, 40% received capecitabine, 30% received other anticancer therapies.

Table 30. Summary of 1st line post study treatment anticancer therapy (ITT Population)

	E7389 (N=554)	Capecitabine (N=548)
Number of subjects who took 1st line anticancer drugs, n(%)	390 (70.4)	340 (62.0)
Taxane	29 (5.2)	65 (11.9)
CISPLATIN W/DOCETAXEL	0	1 (0.2)
DOCETAXEL	11 (2.0)	29 (5.3)
IXABEPILONE	1 (0.2)	8 (1.5)
PACLITAXEL	16 (2.9)	26 (4.7)
TAXANES	0	1 (0.2)
TAXOL W/CARBOPLATIN	1 (0.2)	1 (0.2)
Anthracycline	17 (3.1)	34 (6.2)
Anti-Her2 therapy	11 (2.0)	23 (4.2)
Biologics	9 (1.6)	14 (2.6)
Capecitabine	221 (39.9)	55 (10.0)
Eribulin	1 (0.2)	0
Gemcitabine	35 (6.3)	54 (9.9)
Hormonal Therapy	56 (10.1)	54 (9.9)
Platinum Therapy	35 (6.3)	58 (10.6)
TKI Therapy	4 (0.7)	5 (0.9)
Vinorelbine	63 (11.4)	76 (13.9)
Other	24 (4.3)	43 (7.8)

Source: Study 301 CSR, Table T_ad_OSPFS_8.1.2.2.

Note: By “1st line” it is meant 1st therapy post-study.

A number of analyses were conducted to assess the impact of post-study therapy, , including capecitabine (or eribulin) therapy, and HER2 therapy (data not shown).

Summary of main study

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 31. Summary of Efficacy for trial E7389-G000-301

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		
Study identifier	E7389-G000-301	
Design	Phase 3, open-label, randomized, two-parallel group, multicenter study comparing E7389 with capecitabine in subjects with locally advanced or metastatic breast cancer (MBC). Subjects were randomized to receive either E7389 or capecitabine on a one to one ratio	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	01.04.2006 (FPI) – 12.03.2012 (data cut-off) not applicable not applicable
Hypothesis	Superiority	
Treatment groups	Eribulin 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 eribulin mesilate)	Administered as an IV bolus at 1.23 mg/m^2, administered intravenously over two to five minutes, on Days 1 and 8 of a 21-day cycle. number randomised: 554
	Capecitabine	Administered as an oral administration of 2.5 g/m^2/day administered twice daily in two equal doses on Days 1 to 14 each 21-day cycle. number randomised: 548

Endpoints and definitions	Primary endpoint	OS	OS was measured from the date of randomization until the date of death from any cause.
	Primary endpoint*	PFS	PFS was measured from the date of randomization to the date of recorded progression of the disease or the death of the subject from any cause, whichever occurred first.
	Secondary endpoint	ORR	Objective tumour response was defined as the number of subject with best overall response of complete response (CR) or partial response (PR) divided by the number of subjects in the analysis population. The response rate was based on the independent review of disease assessments and investigator's assessments.
Database lock	14 Jun 2012		
	*Note: There were two primary endpoints. As only one was required to be met in order to conclude a positive study, they are not referred to as co-primary in this assessment report.		

Results and analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability and Effect estimate per comparison	Treatment group	Eribulin	Capecitabine
	Number of subjects	554	548
	OS No of patients with death (%)	446 (80.5)	459 (83.8)
	Median survival in days (95% CI)	484 (462, 536)	440 (400, 487)
	Median survival in months (95% CI)	15.9 (15.2, 17.6)	14.5 (13.1, 16.0)
	p-value (stratified log-rank)[a]	0.0560	
	Hazard Ratio (95% CI) using stratified Cox proportional hazards	0.879 (0.770, 1.003)	
	a: Stratified on HER2/neu status (clinical database) and geographical region		
Analysis description	**Co-Primary analysis**		
Descriptive statistics and estimate variability	**PFS - independent review** No of patients with PFS events (%)	385 (69.5)	360 (65.7)
	Median progression free survival in days (95% CI)	126 (106, 131)	129 (120, 147)

and Effect estimate per comparison	Median progression free survival in months (95% CI)	4.1 (3.5, 4.3)	4.2 (3.9, 4.8)
	p-value	0.3045	
	Hazard Ratio (95% CI) using stratified Cox proportional hazards	1.079 (0.932, 1.250)	
	PFS - investigator review No of patients with PFS events (%)	470 (84.8)	468 (85.4)
	Median progression free survival in days (95% CI)	127 (120, 131)	126 (113, 136)
	Median progression free survival in months (95% CI)	4.2 (3.9, 4.3)	4.1 (3.7, 4.5)
	p-value	0.7361	
	Hazard Ratio (95% CI) using stratified Cox proportional hazards	0.977 (0.857, 1.114)	
Analysis description	**Secondary analysis**		
Descriptive statistics and estimate variability and Effect estimate per comparison	**ORR – independent review**** No of patients with CR + PR (%)	61 (11.0)	63 (11.5)
	95% CI (Exact Pearson-Clopper 2-sided CI)	(8.5, 13.9)	(8.9, 14.5)
	p-value	0.849	
	* Note: the ORR result specified in Section 5.1 of the SmPC is based on randomised patients and not just the response evaluable population		

Supportive studies

The two supportive phase-2 studies in this application (Study 221 and Study 224) are supportive with regard to safety. They were performed in Japan.

The MAH states that the pivotal Study 301 is the sole efficacy trial in support of this type II variation. However, efficacy was a primary objective of Study 221; a brief summary of efficacy results is therefore given below.

Study 221

(Protocol number: E7389-J081-221), n= 84 (81 treated)

"Phase II Clinical Study of E7389 for Locally Advanced or Metastatic Breast Cancer"

This was a Phase 2, open-label, single-arm, uncontrolled, multi-centre study in patients with advanced or relapsed breast cancer who had received up to three prior therapies for advanced or relapsed breast cancer, including an anthracycline and a taxane. Subjects also had to have a life expectancy of 3 months or longer, have adequate renal, liver, and bone marrow function, and no clinically significant therapy-related toxicity at study entry. Eribulin mesilate 1.4 mg/m^2 was administered as an i.v. bolus over 2 to 5 minutes on Days 1 and 8 of each 21-day cycle.

Study 224

(Protocol number: E7389-J081-224), n= 6 (6 treated)

"A Phase 2 Extension Study of E7389 in Patients with Advanced or Relapsed Breast Cancer"

This was an extension of Study 221. Safety and efficacy data are included in the results of Study 221.

Study 221 efficacy results:

Of the 80 subjects in the Full analysis set (FAS), 17 subjects were assessed as objective response cases (PR in all subjects) by Assessment Committee (independent review) and objective response rate (ORR), one of the primary endpoints of this study, was 21.3% (95% confidence interval: 12.9 – 31.8%). In FAS, 47 subjects were assessed as disease control (CR+PR+SD) by the independent review and disease control rate was 58.8% (95% confidence interval: 47.2 – 69.6%) and 22 subjects were assessed as clinical benefit (CR + PR +SD of at least 6 months) and clinical benefit rate was 27.5% (95% confidence interval: 18.1 – 38.6%). For objective response rates by the independent review, the mode of the posterior distribution calculated using Jeffreys non-informative prior distribution [Beta distribution Be (0.5, 0.5)] by Bayesian approach was 20.9%, the predictive posterior probabilities that true objective response rates were lower than 10%, 15% and 20% were 0.1%, 6.4% and 38.0% respectively, and 95% equal tail credible interval and 95% highest posterior density credible interval of true objective response rates were 13.4 – 31.1% and 13.0 – 30.6% respectively. The median (95% confidence interval) of duration of overall response by the independent review was 119.0 days (85.0 – 148.0 days). The median (95% confidence interval) of progression-free survival by the independent review was 112 days (61.0 – 133.0 days), and progression-free survival rates at Month 3, 6, 9 and 12 were 54.2%, 20.1%, 10.1% and 6.7% respectively. Though number of subjects with event (death) was 41 in 80 subjects (51.3%) being small, median (95% confidence interval) of overall survival was 331.0 days (234.0 days – uncalculable), and 6-month and 12-month survival rates were 72.3% and 45.4% respectively. Since the analytical results of the primary and secondary endpoints showed no large differences between FAS and PPS, the selection of analysis sets appeared to have only slight influence on the conclusion concerning the efficacy of eribulin in this study. Subgroup analyses, stratifying FAS by age, tissue types, number of prior chemotherapy regimens, with or without administration of capecitabine and vinorelbine in prior chemotherapy, number of prior chemotherapy regimens for locally advanced or metastatic breast cancer, presence or absence of relapse, presence or absence of primary lesion or metastatic lesion, presence or absence of drug refractory, HER2/neu expression status, and sensitivity to hormones (ER and PgR), were performed, so that no factor appeared to clearly influence the evaluation of efficacy in this study.

It is concluded that the PFS of approximately 3.7 months (112 days) in Study 221 is consistent with the PFS of registration Study 305 (3.6 months) and the current pivotal Study 301 (4.1/4.2 months).

2.4.2. Discussion on clinical efficacy

The sought indication differs from the already approved indication with regard to the required number of prior chemotherapy regimens for advanced disease: one compared with two. This would move the indication up to 2nd line therapy for metastatic/advanced disease compared with the present indication in the 3rd line setting.

Design and conduct of clinical studies

Study 301 was an open-label 1:1 randomised phase III trial performed in patients with locally advanced or metastatic breast cancer who had received up to 3 prior chemotherapy regimens, and no more than two prior regimens for advanced and/or metastatic disease. This includes 1^{st}-2^{nd} line metastatic treatment. The chemotherapy regimens must have included an anthracycline and a taxane, and there must be documented evidence of disease progression during or after their most recent anticancer therapy. Efficacy in patients with active brain or subdural metastases, or with meningeal carcinomatosis has not been evaluated. It is noted that the inclusion requirement to end biological treatment 2 weeks before start of study treatment is not in line with current clinical practice, according to which anti-HER2 therapy should be continued, and would likely not be accepted if the study was initiated today. In this study HER2 positive status was 15% and balanced across arms.

OS and PFS were the two primary endpoints. The overall significance level alpha was 0.05, with 0.04 used on OS, and 0.01 on PFS.

Efficacy data and additional analyses

Baseline characteristics

In total 280/554 (50.54%) of the patients in the eribulin arm were treated in the 2nd-line for metastatic/advanced disease, which represents the new indication sought. Another 116 (20.9%) were treated in the 1st line, thus 396/554 (71.5%) of the patients in the eribulin arm were treated in earlier stages of the disease than the already approved 3rd line indication.

Overall, there were no major imbalances in baseline patient, disease, or tumour characteristics.

Time since original diagnosis was somewhat higher in the eribulin arm (36 months vs. 31 months). HER2 positivity was approximately 15% in both study arms. Oestrogen receptor (ER) and hormone receptor (HR) positivity were somewhat lower (approximately 4%), and triple negativity slightly higher (2.6%) in the eribulin arm compared with the capecitabine arm. The direction of the imbalance for all these prognostic factors could in theory favour the capecitabine arm. However, with regard to disease sites, the capecitabine group had 5% more liver metastasis, and 4% less patients with only 1 organ involved.

There were no major imbalances in the prior anticancer therapies. While the use of prior anti-HER2 therapy in the form of trastuzumab was balanced across study arms (approximately 10% in both), there was an imbalance in the proportion of HER2-positive patients having received prior trastuzumab; 67% in the eribulin arm compared to 59% in the capecitabine arm. This could in theory result in a better response to post-study trastuzumab in the capecitabine arm compared with the eribulin arm, and could thus potentially favour capecitabine in the OS comparison. However, due to the small numbers (the difference between arms representing 1.6% of the ITT) it is not likely to have impacted the overall study results.

Thus, the imbalances seen in baseline characteristics were small, and would mostly be expected to affect the results in favour of capecitabine, if at all. While, in theory, this could explain why a smaller difference than “expected” between arms is seen in PFS, it does not offer an explanation for the differential effects seen in OS vs. PFS. Baseline factors would be expected to affect both outcome measures.

Efficacy results

None of the primary objectives were met. Overall survival (OS) showed a statistically non-significant trend of better outcome for eribulin- compared with capecitabine-treated patients, with a median difference of 1.4 months. For progression-free survival (PFS) there was no difference between arms. This discordance between OS and PFS results was identified as a main issue for the efficacy assessment. However, the OS Kaplan–Meier curves separated at an early time point, and remained separated over time, with median OS at 15.9 months vs. 14.5 months in the in the eribulin and capecitabine arms, respectively, with overlapping 95% CIs and p= 0.0560. The pre-specified p-value to conclude a positive study at this final OS analysis was p<0.0372. I.e. this cannot be considered borderline statistical significance. The numerical difference in medians was thus 1.4 months (44 days), HR was 0.879 (95% CI: 0.770, 1.003). The 1-, 2-, and 3-year survival rates were also numerically higher in the eribulin arm, and statistically significantly higher for 1-year survival rate.

The PFS analyses according to independent review (IRC) and investigator assessments (INV) generated very similar results, with a difference in median PFS of +/- 2-3 days, and HRs 1.079 (95% CI: 0.932, 1.250) and 0.977 (95% CI: 0.857, 1.114), respectively. While the differences between IRC and INV results are small, the difference in uncertainty, as described by the 95% confidence intervals, could be an issue for the B/R balance. Based on the upper 95% confidence limits of the HRs, there is a 2.5% chance/risk that eribulin is up to 11% poorer than capecitabine with regard to PFS according to INV, and up to 25% according to IRC. Overall, there was a 74% concordance between investigator and independent review in detecting patients with or without PD, and no bias in progression date was detected. As no important bias has been identified in the investigator assessments of PFS overall, investigator-based data for PFS is accepted as basis for this discussion.

There were no statistically significant differences in ORRs and CBRs between arms. Numerically slightly higher rates were observed for capecitabine.

The global QoL scores showed no meaningful changes during study, or differences between eribulin and capecitabine. The QoL scores for the separate items are reflective of the ADR profiles, with worse scores for eribulin with regard to systemic therapy effects and hair loss, and worse scores for capecitabine with regard to gastrointestinal ADRs. The QoL data therefore does not impact the B/R balance.

The use of analgesics was slightly higher in the eribulin arm, which could explain a slightly better VAS pain score in this study arm.

ECOG performance status (PS) scores displayed a similar pattern across arms during study. The vast majority of patients remained in PS 0-1 during study, potentially reflecting both effect and tolerability of both treatments.

Subgroup and adjusted analyses

Sought indication

The subgroup with 1 prior chemotherapy regimen for advanced disease, which corresponds to the sought indication, had a HR consistent with the overall results, i.e. OS HR 0.84 (95% CI: 0.698, 1.010), and 49 days' (approximately 1.6 month) median difference in OS favouring eribulin. For PFS the results in this subgroup were also consistent with the overall PFS results, i.e. HR 1.029 (95% CI: 0.838, 1.263), and 2 days' difference in median PFS favouring capecitabine.

Demographic subgroups

OS subgroup analyses showed no major differences between demographic subgroups. The geographic region subgroup Latin America showed a statistically significant better HR for eribulin vs. capecitabine. No other demographic subgroups achieved statistical significance. Western Europe (n= 157, 14% of ITT) and Eastern Europe (n= 612; 55% of ITT) had similar HR point estimates, 0.92 and 0.94, respectively (both n.s.). The combined geographic region north America/Western Europe/Australia (n= 244; 22% of ITT) had a HR point estimate of 0.84, with the small group from North America as the driver of the more favourable HR.

The PFS sub-group analyses of demographics showed a nominally significant HR of 1.27 in favour of capecitabine in the Eastern Europe subgroup, which is the largest geographic region subgroup representing 55.5% of the ITT. This is in contrast with the OS subgroup analysis with a non-significant HR of 0.94.

Comparing Eastern Europe with the rest of the world, it was observed that, irrespective of therapy, more TEAE and serious TEAE in general were reported in the rest of the world. This was the case also for grade 3 palmoplantar erythrodysaesthesia, capecitabine 23% vs. 8%. Furthermore, and in the rest of the world, TEAE led to more discontinuations of capecitabine prior to progression (14% vs. 8%) and dose reductions (42% vs. 24%). In this context it should be remembered that the study dose of capecitabine was 2500 mg/m^2/day, i.e. the licensed dose, a dose considered too high from a tolerability perspective by leading breast cancer experts, at least in the West.

Receptor subgroups and adjusted analyses

The direction of the imbalance for all prognostic factors except performance status (see Disease characteristics) could in theory favour the capecitabine arm. Post-hoc OS analyses adjusted for baseline receptor status were performed. When OS was adjusted post-hoc by oestrogen receptor and triple-negative receptor status, (each factor alone as well as and in combination), improvements in OS for eribulin compared with capecitabine was observed, reaching nominal statistical significance (with p< 0.0372 significance limit). Nominally statistically significant results were also reached for the composite factor Hormone receptor status. The hazard ratios for PFS also showed a numerical improvement after adjustment for the status of these receptors (Table 21). This indicates that the relatively small baseline imbalances in ER and triple-negative receptor status may have affected the study results to some degree.

A large number of other disease or pre-treatment characteristics did not appear to explain the difference in OS between study arms seen in the primary OS analysis, since HRs remained stable around 0.85 – 0.89 when adjusted for these as single variables (Table 22).

However, multi-adjusted post-hoc analyses adjusted for a large number of baseline factors of potential prognostic impact resulted in OS HR 0.94 (95%CI: 0.82, 1.07), PFS (investigator) HR 1.01 (0.89, 1.16), and PFS (IRC) HR 1.11 (0.95, 1.28), respectively. Thus, PFS HRs were virtually unchanged, while OS results deteriorated, indicating that the OS results are less robust than the PFS results.

In subgroup analysis by receptor status, a larger relative OS treatment effect of eribulin compared with capecitabine was seen in the ER negative, hormone receptor (HR) negative and HER2 negative pre-specified subgroups, compared to their complementary receptor positive subgroups, and most of all in the combined triple-negative subgroup of patients: OS HR 0.70 (95% CI: 0.545; 0.91) vs. 0.93 (n.s) in the complementary set). The PFS subgroup analyses showed similar trends of a relatively better outcome for eribulin vs. capecitabine in the triple-negative subgroup and in the HER2-negative subgroup.

However, opposite trends were observed in the updated OS subgroup analysis of the registration Study 305, with better HR point estimates for ER positive, PgR positive and HER2 positive subgroups, compared with their negative counterparts, and better OS HR estimates for the non-triple negative subgroup compared with the triple-negative; 0.77 (95% CI: 0.63; 0.95) vs. 0.89 (95% CI 0.60; 1.32, Figure 6). For PFS, the updated HRs for Study 305, provided in responses to questions, were very similar in triple negative vs. the complementary set, 0.79 vs. 0.78.

The conflicting findings between Study 301 and Study 305 with regard to receptor subgroups weaken the observations made in study 301. Furthermore, pooled data (although questionable from a methodological point of view) for studies 305 and 301 indicated similar effects for HER2-positive and -negative patients, with pooled OS HR 0.82 (95% CI: 0.62; 1.06) and 0.84 (95% CI: 0.74; 0.95), respectively; and pooled PFS HR 1.02 (95% CI: 0.78, 1.34) and 0.84 (95% CI: 0.74, 0.95), respectively. Based on the data from both phase 3 trials in breast cancer, Studies 305 and 301, it is concluded that no relevant difference in efficacy has been shown between the HER2 positive and negative patient subgroups, or between triple negative vs. non- triple negative subgroups.

With regard to disease status factors, patients with non-visceral-only disease (n= 142; 13% of the ITT) were clearly distinguished from the other sub-groups with a statistically significant OS HR at 0.51 (95% CI: 0.33, 0.795). Again the reverse finding was seen in Study 305.

OS - PFS discordance

Explanations for the discrepancy between OS and PFS results were sought.

PFS

The MAH provided analyses of progression of existing lesions or new lesions by IRC and INV. Due to a large proportion of informative censoring in the IRC data and as no important bias has been observed, the use of INV data are accepted in the analysis of censoring patterns.

It was also found that the sites of new metastases differed, but this pattern was not replicated in study 305.

The MAH has presented pre-clinical data suggesting that eribulin treatment may induce a phenotypic change to a more differentiated and less aggressive state, and changes in tumour vasculature making the tumours more accessible to post-progression therapy, thereby presenting plausible biological mechanisms that could to some degree offer theoretical explanations for these findings.

The reason for PFS censoring was new anti-cancer therapy in approximately 20% of patients in both study arms by IRC /ITT. No bias by potential differences in the causes for start of new therapy in the PFS analysis was identified.

The divergent results in Eastern Europe with regard to OS (HR 0.94) and PFS OS (HR 1.27), the contrasting PFS results compared with other geographic subgroups, as well as the more frequent censoring of death in the capecitabine arm driven by the Eastern European region was further investigated. Data indicated that differential informative censoring and imbalances in triple negative status may have contributed to the diverging PFS results seen in Eastern Europe compared with other regions. In addition, the large proportion of patients with unknown HER2 positive status could include an imbalance of the actual HER2 status, if analysed, of potential impact on PFS. However, baseline prognostic factors would also be expected to affect OS. Furthermore, since differential informative censoring was observed also for investigator-based PFS, it cannot explain the PFS-OS discordance.

The MAH explored PFS censoring times by IRC and INV. In the IRC analysis, patients in the capecitabine arm are censored earlier than in the eribulin arm, while time to censoring is the same for INV analysis. The observed differential pattern of time to censoring along with informative censoring could help explain the PFS results based on IRC analysis; however, given that there is no differential pattern observed for investigator assessment, this does not help to explain the discordance in OS and PFS results in general.

PFS2 data were not available and the substitute analysis performed by the MAH did not add any new information.

OS

The analysis of post- study therapy as cause for the difference seen in OS between study arms, favouring eribulin, such as the impact of any post- study anti-cancer therapy (yes/no), the impact of post- study capecitabine use, and of anti-HER2 use, could not explain the difference in OS.

The qualitative difference in metastatic sites and their different prognosis post-progression could potentially offer an explanation for a smaller part of the PFS-OS discrepancy (see above).

Supportive studies

The PFS of approximately 3.7 months (112 days) in Study 221 is consistent with the PFS of registration Study 305 (3.6 months) and the current pivotal Study 301 (4.1/4.2 months).

2.4.3. Conclusions on the clinical efficacy

The study objective was not met, since superiority of eribulin over capecitabine was not demonstrated in the studied disease setting, which includes the sought indication 2nd line metastatic therapy. There is a trend, however, of numerically better OS in the eribulin arm potentially suggesting that eribulin is not inferior to capecitabine in this disease setting. For PFS, no clinically relevant or statistically significant differences between arms were seen.

Based on the investigator assessments of PFS the HR at 0.98 and the narrow 95% confidence interval (0.86, 1.11), it is considered that a clinically relevant difference can be excluded.

The discrepancy between OS and PFS data are problematic since potentially suggesting that factors other than the study treatments might be affecting the results. The MAH has provided a large number of analyses investigating this issue, however there was no clear explanation of this discrepancy.

There was a qualitative difference between study arms in the type of new metastasis in those 55% of patients (by INV) who had new lesion as progression event, where the prognosis is expected to be worse for those metastasis sites more frequently seen for capecitabine. However, at this stage it is not known if this difference in metastasis location is a mere chance finding, or if it represents a true difference in effect.

2.5. Clinical safety

2.5.1. Introduction

- Safety analysis populations

The safety assessment is based on a total of 1503 patients treated in seven phase 2-3 trials in metastatic/advanced breast cancer (Table 32). This pooled safety population will be referred to as the Breast Cancer Population (BCP).

Of the studies included in the BCP, studies 305, 201 and 211 were assessed at initial market approval; the neuropathy study 209 comparing eribulin and ixabepilone was assessed in FUM 015; while the pooled data from studies 221 and 224 are assessed for the first time within the present application, together with the pivotal study 301. A description of the studies is given in Table 33 below.

Table 32. Safety populations

Safety population	Phase	Trial name	Treatments	Number of eribulin-treated subjects
Breast Cancer Population (BCP).	Phase 3	Study 301	Eribulin vs. capecitabine.	544
		Study 305 "EMBRACE"	Eribulin vs. treatment of physician's choice (TPC).	503
	Phase 2	Study 201 [a]	Single-arm eribulin	33
		Study 209	Eribulin vs. ixabepilone	51
		Study 211	Single-arm eribulin	291
		Study 221	Single-arm eribulin, pooled	81
		Study 224 [b]		(6) included in 81 above
	Total			1503

a: Subjects who received 28-day cycles of eribulin in Study 201 have been excluded from the analysis.
b: The six subjects who continued to receive eribulin in extension Study 224 after receiving eribulin in Study 221 are included in the total of 81 treated subjects for Study 221. Data from Study 221 were pooled with the data from Study 224, once all enrolled subjects had discontinued treatment in Study 224.
For complete protocol numbers, please refer to

Table 33. Completed Breast Cancer Trials Included in the Safety Analysis of Eribulin

Study ID/ Status	No. of Study Centers (Location)	Indication	Study Design Control Type	Study Drug Dose, Route, and Regimen	Subjects Enrolled/ Treated by Treatment Arm	Median Age (range), y
Primary Efficacy and Safety Study						
E7389-G000-301 Clinical cut off date: 12 Mar 2012 DBL: Jun 2012	272 initiated (North and South America, Europe, Asia, South Africa and Australia)	Metastatic or locally advanced BC previously treated with anthracyclines and taxanes	Phase 3, randomized, open-label, active-controlled, parallel group; prestratified based on geographic region and HER2 status	Eribulin mesilate 1.4 mg/m^2 Capecitabine 2.5 g/m^2/day Eribulin i.v. bolus over 2-5 minutes on Days 1 and 8 of each 21-day cycle until disease progression. Capecitabine administered p.o. twice daily in 2 equal doses on Days 1 to 14 each 21-day cycle.	1102 enrolled Eribulin: 554 enrolled 544 treated Capecitabine: 548 enrolled 546 treated	 Eribulin: 54 (24-80) Capecitabine: 53 (26-80)
Supportive Safety Studies						
E7389-G000-305 [a,b] Clinical cut off dates: May 2009 (original) Nov 2012 (Type II variation) DBL: 14 Nov 2012	149 initiated (19 countries in North and South America, Africa, Europe, Asia, and Australia)	Locally recurrent or metastatic BC following 2 to 5 prior chemotherapy regimens (including an anthracycline & taxane)	Phase 3, open-label, randomized (2:1 vs. TPC), parallel group	Eribulin mesilate 1.4 mg/m^2 Treatment of Physician's Choice Eribulin i.v. bolus over 2-5 minutes on Days 1 and 8 of each 21-day cycle until disease progression.	762 enrolled[b] Eribulin 508 enrolled 503 treated TPC: 254 enrolled 247 treated	 Eribulin: 55 (28-85) TPC: 56 (27, 81)
E7389-A001-201[a] Completed	23 (US)	Advanced/ metastatic recurrent or refractory BC after an anthracycline & taxane	Phase 2, open-label, single-arm. Simon's 2-stage optimal design	Eribulin mesilate 1.4 mg/m^2 i.v. bolus over 2-5 minutes Arm 1: eribulin on Days 1, 8, and 15 of a 28-day cycle (excluded from ISS analysis) (N=70) Arm 2: eribulin on Days 1 and 8 of each 21-day cycle (N=33)	104 enrolled 103 treated 28-day: 70 21-day: 33	55 (32-84) 28-day: 55 (34-84) 21-day: 52 (32-81)
E7389-G000-209 Completed	48 (US)	Advanced BC to compare the incidence of neuropathy AEs	Phase 2, randomized, open-label, 2-arm, active control	Eribulin mesilate 1.4 mg/m^2 Ixabepilone 32 or 40 mg/m^2 Eribulin i.v. bolus over 2-5 minutes on Days 1 and 8 of each 21-day cycle Ixabepilone by i.v. infusion over 3 h on Day 1 of each 21-day cycle	Planned: 98 Treated: 101 Eribulin: 51 Ixabepilone: 50	Eribulin: 53 (24 – 73) Ixabepilone: 57 (33 – 79)
E7389-G000-211[a] Completed	82 (US, Western Europe, Canada)	Locally advanced or metastatic BC following anthracycline, taxane, & capecitabine	Phase 2, open-label, single-arm, uncontrolled	Eribulin mesilate 1.4 mg/m^2 i.v. bolus over 2-5 minutes on Days 1 and 8 of each 21-day cycle until disease progression	299 enrolled 291 treated	56 (26-80)
E7389-J081-221 Completed	22 (Japan)	Advanced or relapsed BC	Phase 2, open-label, single-arm, uncontrolled	Eribulin mesilate 1.4 mg/m^2 i.v. bolus over 2-5 minutes on Days 1 and 8 of each 21-day cycle until disease progression	84 enrolled 81 treated (includes 6 who continued in Study 224)	54 (31-72)
E7389-J081-224 Completed	5 (Japan)	Advanced or relapsed BC	Phase 2 extension of Study 221	Eribulin mesilate 1.4 mg/m^2 i.v. bolus over 2-5 minutes on Days 1 and 8 of each 21-day cycle until disease progression	6 (continued from Study 221)	51 (31 – 68)

AE = adverse event; BC = breast cancer; DBL = database lock; ISS = Integrated Safety Summary; i.v.= intravenous; MAA = Marketed Authorisation Application; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; p.o. = per os (oral); s.c. = subcutaneous; SCS = Summary of Clinical Safety; TPC = Treatment of Physician's Choice; US = United States; y = years.
a: Study was previously submitted as part of the original MAA for eribulin.
Source: Modified from SCS, Table 2.(Column for distribution of race not included)

Safety assessments and definitions

- Study 301 safety assessments

Safety assessments included monitoring the incidence and severity of AEs, clinical laboratory test results, vital signs measurements, physical examination findings, electrocardiogram (ECG) readings, and concomitant medication use. Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that was being reported as an AE, were considered an AE if the QTc interval was >450 msec and there was an increase of >60 msec from Baseline. Also, any ECG abnormality that the investigator considered an AE was reported as such.

- Definition of TEAE in Study 301

"A treatment-emergent AE (TEAE) was defined as an AE that emerged during treatment, having been absent at pre-treatment (baseline) or re-emerged during treatment, having been present at pre-treatment (baseline) but stopped before treatment, or worsened in severity during treatment relative to the pre-treatment state, when the AE was continuous.

Only those AEs that were treatment-emergent were included in summary tables. All AEs, treatment-emergent or otherwise, were presented in subject data listings. Adverse events were regarded as TEAEs if they started on or after the date and time of administration of the first dose of study drug until 30 days after last dose or if they were present prior to the administration of the first dose of study drug and increased in severity during the study."

It is found acceptable to focus on the TEAE as all AE emerging within 30 days after last dose is included taking into consideration that the terminal half-life is approximately 40 h.

- Adverse Events of Special Interest

Asthenia and fatigue (combined), arthralgia and myalgia (combined), alopecia, neutropenia, and peripheral neuropathy were identified as special adverse events of interest (AEIs).

These are presented in the overall AE tables by MedDRA SOC and preferred term.

Two definitions were used to determine the incidence of peripheral neuropathy. The first definition ("narrow SMQ analysis") included the following combined terms contained in the SMQ for neuropathy: neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paraesthesia. The second definition ("broad SMQ analysis") included the list of preferred terms contained in the narrow SMQ for neuropathy as well as the following additional preferred terms: neuropathy, hyperesthesia, painful response to normal stimuli, pallanaesthesia and allodynia. The incidence of peripheral neuropathy based on the two SMQ definitions (narrow and broad) is included in the AE tables.

Patient exposure

The exposure was overall very consistent across eribulin studies 301 and 305, and the pooled phase 2/3 BCP. Study 301 had 1 cycle higher median number of cycles and 1 week longer duration of exposure than Study 305, compatible with the somewhat earlier disease setting. (The median number of prior chemotherapy regimens was 2 in Study 301 compared with 4 in Study 305). Median dose intensity, relative dose intensity and cumulative dose were very similar between the two studies, however, and only cumulative dose was slightly lower in the BCP (Table 34).

Similarly, the dose modification patterns were very consistent across the eribulin safety populations, with the proportions having any dose modification at around 50% in all three populations, time to first dose reduction and dose delay around 15-16 weeks in all three populations, and dose omissions (day 8 dose) around 10% in all populations (

Table 35).

These similarities in exposure and dose modification patterns across studies are consistent with overall similar efficacy and safety findings.

Table 34. Extent of Exposure to Eribulin– Phase 2 / 3 Breast Cancer Trials (Safety Population)

Parameter	All Eribulin-treated Subjects in Study 301 (N=544)	All Eribulin-treated Subjects in Study 305 (N=503)	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503)
Number of cycles received			
n	544	503	1503
Mean (SD)	7.7 (7.88)	6.2 (4.19)	6.5 (6.01)
Median	6.0	5.0	5.0
Q1 – Q3	3 – 9	3 – 9	3 – 8
Min, Max	1, 65	1, 23	1, 65
Duration of exposure (weeks)[a]			
n	544	503	1503
Mean (SD)	24.2 (24.70)	19.6 (13.23)	20.5 (18.96)
Median	17.9	16.9	15.7
Q1 – Q3	10 – 29	9 – 27	9 – 26
Min, Max	3, 196	3, 71	3, 196
Dose Intensity ($mg/m^2/wk$)[b]			
n	544	502	1502
Mean (SD)	0.81 (0.136)	0.78 (0.166)	0.80 (0.152)
Median	0.86	0.85	0.86
Q1 – Q3	0.73 - 0.92	0.68 - 0.92	0.70 - 0.92
Min, Max	0.42, 0.99	0.24, 1.01	0.24, 1.01
Relative Dose Intensity[c]			
n	544	502	1502
Mean (SD)	0.87 (0.146)	0.84 (0.178)	0.86 (0.163)
Median	0.92	0.91	0.92
Q1 – Q3	0.78 - 0.99	0.73 - 0.99	0.75 - 0.99
Min, Max	0.45, 1.06	0.25, 1.08	0.25, 1.08
Cumulative Dose Received (mg/m^2)			
n	544	503	1503
Mean (SD)	19.4 (20.30)	15.8 (10.92)	16.4 (15.40)
Median	13.8	13.7	12.3
Q1 – Q3	7.3 - 22.4	8.0 - 21.6	6.3 - 20.2
Min, Max	1.4, 182.3	1.3, 63.1	1.3, 182.3

Max = maximum, Min = minimum; Q = quartile; SD = standard deviation.
a: Duration of exposure = (Date of Day 1 of last cycle – date of first dose + length of cycle) ÷ 7.
b: Dose intensity = Total dose received ÷ duration of exposure.
c: Relative dose intensity = Dose intensity ÷ planned dose intensity.
Source: SCS, Table 4.

Table 35. Eribulin Dose Modifications - Phase 2/3 Breast Cancer Trials (Safety Population)

Parameter	All Eribulin-treated Subjects in Study 301 (N=544)	All Eribulin-treated Subjects in Study 305 (N=503)	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503)
Any dose modification, overall [a]	293/544 (53.9)	249/503 (49.5)	762/1503 (50.7)
Dose reductions, overall	181/544 (33.3)	155/503 (30.8)	464/1503 (30.9)
Time to first dose reduction, median (weeks)	16.14	15.29	15.14
Dose delays, overall	222/544 (40.8)	170/503 (33.8)	528/1503 (35.1)
Time to first dose delay, median (weeks)	16.14	15.14	15.14
Dose omissions, overall [b]	61/544 (11.2)	43/503 (8.5)	194/1503 (12.9)

a: Dose modifications include interruptions, delays, omissions, and reductions.
b: A dose "omission" in Studies 301 and 305 was defined as a missed dose on Study Day 8.
Source: SCS, Table 5 (abbreviated).

Table 36. Extent of Exposure in Eribulin and Capecitabine study arms (Safety Population)

Extent of Exposure	Treatment Group	
	E7389 (N=544) n (%)	Capecitabine (N=546) n (%)
Number of cycles received		
1	28 (5.1)	47 (8.6)
2	90 (16.5)	104 (19.0)
3	22 (4.0)	36 (6.6)
4	98 (18.0)	71 (13.0)
5	31 (5.7)	18 (3.3)
6	76 (14.0)	55 (10.1)
7	17 (3.1)	16 (2.9)
8	41 (7.5)	41 (7.5)
9	9 (1.7)	8 (1.5)
10	26 (4.8)	35 (6.4)
11 to 20	76 (14.0)	76 (13.9)
21 to 30	16 (2.9)	21 (3.8)
>30	14 (2.6)	18 (3.3)
Median (min, max)	6.0 (1, 65)	5.0 (1, 61)
Duration of treatment[a] (days)		
Mean (SD)	169.1 (172.9)	172.6 (182.8)
Median	125.0	119.0
Min, Max	21, 1372	21, 1442
Actual dose intensity (mg/m^2/week)[b] (%)		
Mean (SD)	0.81 (0.136)	9983.86 (1814.274)
Median	0.86	10524.40
Min, Max	0.4, 1.0	1694.3, 12455.7
Relative dose intensity[c] (%)		
Mean (SD)	0.87 (0.146)	0.86 (0.156)
Median	0.92	0.90
Min, Max	0.4, 1.1	0.1, 1.1
Subjects with dose interruption[d]	7 (1.3)	--
Subjects with dose omission	61 (11.2)	--

a: For E7389, duration of treatment = last cycle Day 1 – date of first dose + 21, if day 1 was last dose of last cycle. For capecitabine, duration of treatment = last cycle Day 1 – date of first dose + 21.
b: Actual dose intensity (mg/m^2/week) = total dose received during study / (duration of treatment in days/7).
c: Relative dose intensity = actual dose intensity (mg/m^2/week) / Planned dose intensity. Planned dose intensity (E7389) = 1.4*2/3 = 0.933 (mg/m^2/week). Planned dose intensity (capecitabine) = 2500*14/3 = 11667 (mg/m^2/week).
d: Dose interruption and omission were summarized only for E7389. Dose interruptions due to a treatment-emergent adverse event were summarized for the E7389 and capecitabine treatment groups. Omissions were only considered at Day 8.
Max = maximum, Min = minimum, SD = standard deviation.

Source: Study 301 CSR, Table 30.

Adverse events

Table 37. Overview of Treatment-Emergent Adverse Events that Occurred in Eribulin-treated Subjects – Phase 2 / 3 Breast Cancer Trials, Safety Population

Category	All Eribulin-treated Subjects in Study 301 (N=544)	All Eribulin-treated Subjects in Study 305 (N=503)	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503)
All TEAEs	512 (94.1)	497 (98.8)	1464 (97.4)
Treatment-related TEAEs[a]	460 (84.6)	474 (94.2)	1381 (91.9)
Severe (Grade 3-4) TEAEs	352 (64.7)	344 (68.4)	1065 (70.9)
Treatment-related Grade 3-4 TEAEs	311 (57.2)	291 (57.9)	925 (61.5)
Serious TEAEs[b]	95 (17.5)	126 (25.0)	352 (23.4)
Serious treatment-related TEAEs[a]	42 (7.7)	58 (11.5)	162 (10.8)
TEAEs with outcome of death[c]	26 (4.8)	20 (4.0)	67 (4.5)
Deaths reported as treatment related[a]	5 (0.9)	5 (1.0)	11 (0.7)
TEAEs leading to treatment discontinuation	43 (7.9)	67 (13.3)	157 (10.4)
Related TEAEs leading to treatment discontinuation[a]	31 (5.7)	45 (8.9)	100 (6.7)
TEAEs leading to dose modification:			
TEAEs leading to dose reduction	172 (31.6)	98 (19.5)	323 (21.5)
TEAEs leading to dose interruption	10 (1.8)	25 (5.0)	58 (3.9)
TEAEs leading to dose delay	173 (31.8)	177 (35.2)	469 (31.2)
Other TEAEs of special interest			
Asthenia/fatigue combined	165 (30.3)	269 (53.5)	723 (48.1)
Peripheral neuropathy (broad SMQ analysis)	149 (27.4)	210 (41.7)	541 (36.0)
Peripheral neuropathy (narrow SMQ)	116 (21.3)	174 (34.6)	446 (29.7)
Arthralgia/myalgia combined	66 (12.1)	110 (21.9)	293 (19.5)

MedDRA version 14.1.
For each row category, a subject with more than one TEAE in that category is counted only once.
CRF = case report form; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standard MedDRA query; TEAE = treatment-emergent adverse event.

a: Includes TEAEs considered by the investigator to be possibly or probably related to study drug or TEAEs with missing causality.

b: Includes deaths.

c: Information obtained from the Adverse Event page of the CRF, and includes subjects who had an ongoing AE at the time of death, and does not reflect the primary reason for death (i.e., disease progression, toxicity, or "other") from the Death page of the CRF.

Source: SCS, Table 12.

Table 38. Study 301, Overview of Treatment Emergent Adverse Events for Eribulin and Capecitabine

Category	Treatment Groups	
	E7389 (N=544) n (%)	Capecitabine (N=546) n (%)
TEAEs[a]	512 (94.1)	494 (90.5)
Treatment-related TEAEs[b, c]	460 (84.6)	421 (77.1)
TEAEs with CTCAE Grade 3 or above[d]	356 (65.4)	251 (46.0)
Serious TEAEs	95 (17.5)	115 (21.1)
Deaths	26 (4.8)	36 (6.6)
Other SAEs		
Life threatening	12 (2.2)	19 (3.5)
Required inpatient hospitalization or prolongation of existing hospitalization	73 (13.4)	93 (17.0)
Persistent or significant disability or incapacity	3 (0.6)	2 (0.4)
Other important medical event	9 (1.7)	3 (0.5)
TEAEs leading to study drug dose adjustment		
TEAEs leading to study drug withdrawal	43 (7.9)	57 (10.4)
TEAEs leading to study drug dose interruption	10 (1.8)	1 (0.2)
TEAEs leading to study drug dose reduction	174 (32.0)	174 (31.9)
TEAEs leading to study drug dose delay	173 (31.8)	195 (35.7)

AE = adverse event, CTCAE = Common Toxicity Criteria for Adverse Events, SAE = serious adverse event, TEAE = treatment-emergent adverse event.
a: Adverse events that started on or after the first dose of study drug and within 30 days after the date of the last dose, or started before the first dose of study drug, but worsened after the first dose and within 30 days after the last dose of study drug.
b: Treatment–related TEAEs included TEAEs that were considered by the investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
c: A subject with two or more AEs or SAEs was counted only once in that category.
d: Adverse events were graded using CTCAE version 3.0.

Source: Study 301 CSR, Table 31.

TEAEs of any grade in Study 301

Table 39. TEAEs Occurring in 10% or More of Eribulin-treated Subjects by System Organ Class and Preferred Term – in pivotal Study 301 and Phase 2/3 Breast Cancer Trials

MedDRA SOC Preferred term	Study 301		Study 305	Pooled Phase 2/3 Breast Cancer Trials
	Capecitabine (N=546)	Eribulin (N=544)	Eribulin (N=503)	Eribulin (N=1503)
Patients with any TEAE	494 (90.5)	512 (94.1)	497 (98.8)	1464 (97.4)
Blood and Lymphatic System Disorders	**173 (31.7)**	**345 (63.4)**	**308 (61.2)**	**994 (66.1)**
Neutropenia	87 (15.9)	295 (54.2)	260 (51.7)	857 (57.0)
Leukopenia	57 (10.4)	171 (31.4)	117 (23.3)	441 (29.3)

Anemia	96 (17.6)	104 (19.1)	94 (18.7)	311 (20.7)
Gastrointestinal Disorders	**287 (52.6)**	**239 (43.9)**	**308 (61.2)**	**908 (60.4)**
Nausea	133 (24.4)	121 (22.2)	174 (34.6)	509 (33.9)
Constipation	47 (8.6)	42 (7.7)	124 (24.7)	296 (19.7)
Diarrhoea	157 (28.8)	78 (14.3)	92 (18.3)	270 (18.0)
Vomiting	92 (16.8)	65 (11.9)	91 (18.1)	264 (17.6)
General Disorders and Administration Site Conditions	**209 (38.3)**	**248 (45.6)**	**351 (69.8)**	**970 (64.5)**
Asthenia + Fatigue	152 (27.8)	165 (30.3)	269 (53.5)	723 (48.1)
Fatigue	84 (15.4)	91 (16.7)	146 (29.0)	420 (27.9)
Asthenia	79 (14.5)	83 (15.3)	135 (26.8)	339 (22.6)
Pyrexia	31 (5.7)	70 (12.9)	105 (20.9)	306 (20.4)
Investigations	**91 (16.7)**	**113 (20.8)**	**182 (36.2)**	**435 (28.9)**
Weight decreased	18 (3.3)	20 (3.7)	107 (21.3)	171 (11.4)
Metabolism and Nutrition Disorders	**142 (26.0)**	**127 (23.3)**	**175 (34.8)**	**521 (34.7)**
Decreased appetite	81 (14.8)	68 (12.5)	113 (22.5)	329 (21.9)
Musculoskeletal and Connective Tissue Disorders	**152 (27.8)**	**187 (34.4)**	**266 (52.9)**	**706 (47.0)**
Arthralgia + Myalgia	38 (7.0)	66 (12.1)	110 (21.9)	293 (19.5)
Back pain	43 (7.9)	56 (10.3)	78 (15.5)	196 (13.0)
Arthralgia	31 (5.7)	42 (7.7)	70 (13.9)	191 (12.7)
Pain in extremity	37 (6.8)	47 (8.6)	57 (11.3)	150 (10.0)
Nervous System Disorders	**152 (27.8)**	**213 (39.2)***	**308 (61.2)**	**802 (53.4)**
Peripheral neuropathy, based on broad SMQ	75 (13.7)	149 (27.4)	210 (41.7)	541 (36.0)
Peripheral neuropathy based on narrow SMQ [a]	59 (10.8)	116 (21.3)	174 (34.6)	446 (29.7)
Headache	57 (10.4)	69 (12.7)	97 (19.3)	258 (17.2)
Peripheral sensory neuropathy	38 (7.0)	73 (13.4)	62 (12.3)	187 (12.4)
Respiratory, Thoracic, and Mediastinal Disorders	**124 (22.7)**	**128 (23.5)**	**189 (37.6)**	**519 (34.5)**
Dyspnoea	59 (10.8)	56 (10.3)	79 (15.7)	211 (14.0)
Cough	44 (8.1)	45 (8.3)	72 (14.3)	204 (13.6)
Skin and Subcutaneous Tissue Disorders	**288 (52.7)**	**230 (42.3)**	**266 (52.9)**	**792 (52.7)**
Alopecia	22 (4.0)	188 (34.6)	224 (44.5)	672 (44.7)
Palmar-plantar erythrodysaesthesia	246 (45.1)	1 (0.2)	7 (1.4)	15 (1.0)

MedDRA version 14.1.
For each row category, a subject with more than one TEAE in that category is counted only once.

Note: Number (percentage) of subjects in each SOC represents all subjects with TEAEs in that SOC. Only those preferred terms for TEAEs that occurred in ≥10% of subjects in Phase 2/3 Breast Cancer Trials are included in this table. Display is in alphabetical order by SOC, then by decreasing order of frequency of preferred terms within each SOC for the 'Phase 2/3 Breast Cancer Trials' population.
MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standard MedDRA query; SOC = system organ class, TEAE = treatment-emergent adverse event.
a: Based on narrow SMQ analysis. Terms include neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paraesthesia.
*: 210 (38.6) according to Study 301 CSR,Table 32
Source: SCS, Table 13 (eribulin). Study 301 CSR, Table 32(capecitabine).

While not shown in the table above, the incidence of cardiac SOC TEAEs was similar for eribulin (n=34, 6.3%) and capecitabine (n=31, 5.7%).

Severe (grade 3-4) TEAEs

See tables below.

Table 40. Severe (Grade 3-4) TEAEs Occurring in Approximately 1% or More of Eribulin-treated Subjects by SOC and PT – Phase 2/3 Breast Cancer Trials

MedDRA System Organ Class Preferred Term	All Eribulin-treated Subjects in Study 301 (N=544) n (%)	All Eribulin-treated Subjects in Study 305 (N=503) n (%)	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503) n (%)
Subjects with any Grade 3-4 TEAE	330 (60.7)	327 (65.0)	1008 (67.1)
Blood and Lymphatic System Disorders	**267 (49.1)**	**250 (49.7)**	**807 (53.7)**
Neutropenia	249 (45.8)	227 (45.1)	746 (49.6)
Leukopenia	82 (15.1)	70 (13.9)	259 (17.2)
Febrile neutropenia	11 (2.0)	22 (4.4)	68 (4.5)
Anemia	11 (2.0)	10 (2.0)	31 (2.1)
Lymphopenia	1 (0.2)	6 (1.2)	20 (1.3)
Gastrointestinal Disorders	**20 (3.7)**	**24 (4.8)**	**84 (5.6)**
Abdominal pain	4 (0.7)	5 (1.0)	19 (1.3)
Nausea	1 (0.2)	6 (1.2)	18 (1.2)
Vomiting[a]	2 (0.4)	5 (1.0)	14 (0.9)
General Disorders and Administration Site Conditions	**42 (7.7)**	**65 (12.9)**	**173 (11.5)**
Asthenia + Fatigue	33 (6.1)	51 (10.1)	123 (8.2)
Asthenia	23 (4.2)	33 (6.6)	78 (5.2)
Fatigue	11 (2.0)	18 (3.6)	46 (3.1)
Mucosal inflammation	2 (0.4)	6 (1.2)	16 (1.1)
Pain	0	2 (0.4)	15 (1.0)
Investigations	**35 (6.4)**	**29 (5.8)**	**105 (7.0)**
ALT increased	18 (3.3)	9 (1.8)	33 (2.2)
AST increased	8 (1.5)	6 (1.2)	23 (1.5)
GGT increased[a]	1 (0.2)	1 (0.2)	14 (0.9)
Neutrophil count decreased[a]	3 (0.6)	4 (0.8)	14 (0.9)
WBC count decreased[a]	4 (0.7)	4 (0.8)	14 (0.9)
Metabolism and Nutrition Disorders	**29 (5.3)**	**34 (6.8)**	**98 (6.5)**
Hypokalemia	5 (0.9)	13 (2.6)	28 (1.9)
Hyperglycemia	8 (1.5)	6 (1.2)	19 (1.3)
Musculoskeletal and Connective Tissue Disorders	**31 (5.7)**	**28 (5.6)**	**93 (6.2)**
Bone pain	11 (2.0)	10 (2.0)	26 (1.7)
Back pain	8 (1.5)	5 (1.0)	24 (1.6)
Arthralgia + Myalgia	5 (0.9)	2 (0.4)	16 (1.1)
Arthralgia[a]	4 (0.7)	2 (0.4)	13 (0.9)
Nervous System Disorders	**54 (9.9)**	**61 (12.1)**	**164 (10.9)**
Peripheral neuropathy (broad SMQ)	38 (7.0)	45 (8.9)	116 (7.7)
Peripheral neuropathy (narrow SMQ)	33 (6.1)	42 (8.3)	104 (6.9)
Peripheral sensory neuropathy	19 (3.5)	9 (1.8)	36 (2.4)
Neuropathy peripheral	1 (0.2)	17 (3.4)	30 (2.0)
Paraesthesia	5 (0.9)	8 (1.6)	18 (1.2)
Peripheral motor neuropathy	4 (0.7)	8 (1.6)	16 (1.1)
Respiratory, Thoracic, and Mediastinal Disorders	**22 (4.0)**	**27 (5.4)**	**76 (5.1)**
Dyspnoea	12 (2.2)	18 (3.6)	48 (3.2)

MedDRA version 14.1.

For each TEAE, a subject who had more than one episode is counted only once using the event with the highest CTC grade.

For the preferred term 'febrile neutropenia,' severity was converted into CTC grades as follows: mild or moderate = Grade 3, severe = Grade 4, fatal = Grade 5.

For the preferred term 'alopecia,' severity was converted into CTC grades as follows: mild or moderate = Grade 1, severe = Grade 2.

The table is based on the grade 3-4 frequencies in the Phase2/3 population. TEAEs with a frequency < 1% in this population but higher in Studies 301 or 305 are not shown, e.g. diarrhoea. (0.8% in Phase 2/3, 1.1% in Study301).

a: Term included for completeness even though incidence in Phase 2/3 breast cancer trials was <1%.

Source: SCS, Table 15.

Note: MedDRA version 14.1.

For each TEAE, a subject who had more than one episode is counted only once using the event with the highest CTC grade.

For the preferred term ‘febrile neutropenia,’ severity was converted into CTC grades as follows: mild or moderate = Grade 3, severe = Grade 4, fatal = Grade 5.
For the preferred term ‘alopecia,’ severity was converted into CTC grades as follows: mild or moderate = Grade 1, severe = Grade 2.
The table is based on the grade 3-4 frequencies in the Phase2/3 population. TEAEs with a frequency < 1% in this population but higher in Studies 301 or 305 are not shown, e.g. diarrhoea. (0.8% in Phase 2/3, 1.1% in Study301).
a: Term included for completeness even though incidence in Phase 2/3 breast cancer trials was <1%.
Source: SCS, Table 15.

Table 41. Study 301, TEAEs by Severity: Grade ≥ 3

MedDRA Preferred term	E7389 (N=544) n (%)		Capecitabine (N=546) n (%)	
	Total	Related	Total	Related
Subjects with any TEAE Grade ≥ 3	356 (65.4)	311 (57.2)	251 (46.0)	174 (31.9)
Blood and lymphatic system disorders	**267 (49.1)**	**259 (47.6)**	**47 (8.6)**	**44 (8.1)**
Neutropenia	249 (45.8)	245 (45.0)	27 (4.9)	26 (4.8)
Leukopenia	82 (15.1)	81 (14.9)	11 (2.0)	11 (2.0)
Anaemia	11 (2.0)	9 (1.7)	6 (1.1)	4 (0.7)
Febrile neutropenia	11 (2.0)	10 (1.8)	5 (0.9)	5 (0.9)
thrombocytopenia	2 (0.4)	2 (0.4)	6 (1.1)	6 (1.1)
Nervous system disorders	**54 (9.9)**	**38 (7.0)**	**25 (4.6)**	**6 (1.1)**
Peripheral sensory neuropathy	19 (3.5)	18 (3.3)	3 (0.5)	3 (0.5)
General disorders and administration site conditions	**45 (8.3)**	**30 (5.5)**	**48 (8.8)**	**19 (3.5)**
Asthenia	23 (4.2)	16 (2.9)	20 (3.7)	8 (1.5)
Fatigue	11 (2.0)	9 (1.7)	13 (2.4)	6 (1.1)
Investigations	**35 (6.4)**	**27 (5.0)**	**17 (3.1)**	**6 (1.1)**
Alanine aminotransferase increased	18 (3.3)	17 (3.1)	3 (0.5)	2 (0.4)
Aspartate aminotransferase increased	8 (1.5)	6 (1.1)	6 (1.1)	3 (0.5)
Musculoskeletal and connective tissue disorders	**31 (5.7)**	**4 (0.7)**	**16 (2.9)**	**1 (0.2)**
Bone pain	11 (2.0)	0	5 (0.9)	0
Back pain	8 (1.5)	1 (0.2)	3 (0.5)	0
Respiratory, thoracic and mediastinal disorders	**30 (5.5)**	**7 (1.3)**	**35 (6.4)**	**3 (0.5)**
Dyspnea	16 (2.9)	4 (0.7)	24 (4.4)	1 (0.2)
Respiratory failure	5 (0.9)	0	6 (1.1)	0
Metabolism and nutrition disorders	**29 (5.3)**	**11 (2.0)**	**36 (6.6)**	**16 (2.9)**
Hyperglycaemia	8 (1.5)	1 (0.2)	3 (0.5)	2 (0.4)
Hypokalaemia	5 (0.9)	2 (0.4)	11 (2.0)	3 (0.5)
Decreased appetite	3 (0.6)	1 (0.2)	9 (1.6)	6 (1.1)
Dehydration	1 (0.2)	1 (0.2)	8 (1.5)	3 (0.5)
Gastrointestinal disorders	**21 (3.9)**	**13 (2.4)**	**50 (9.2)**	**42 (7.7)**
Diarrhoea	6 (1.1)	5 (0.9)	29 (5.3)	26 (4.8)
Hepatobiliary disorders	**14 (2.6)**	**10 (1.8)**	**12 (2.2)**	**7 (1.3)**
Hepatotoxicity	6 (1.1)	5 (0.9)	2 (0.4)	2 (0.4)
Hyperbilirubinaemia	2 (0.4)	1 (0.2)	6 (1.1)	3 (0.5)
Neoplasm benign, malignant and unspecified	**12 (2.2)**	**0**	**18 (3.3)**	**0**
Neoplasm malignant	7 (1.3)	0	2 (0.4)	0
Tumour pain	3 (0.6)	0	7 (1.3)	0
Skin and subcutaneous tissue disorders	**2 (0.4)**	**1 (0.2)**	**81 (14.8)**	**79 (14.5)**
Palmar-plantar erythrodysaesthesia	0	0	79 (14.5)	78 (14.3)

Note: Subjects with two or more adverse events in the same with the same preferred term are counted only once for that preferred term. Adverse Event terms were coded using Medical Dictionary for Drug Regulatory Affairs (MedDRA) version 14.1. Adverse events were graded using CTCAE version 3.0 per protocol. Treatment-related treatment-emergent adverse events (TEAEs) include TEAEs that were considered by the investigator to be possibly or probably related to study drug or TEAEs with a missing causality.
Source: Study 301 CSR, Table 35.

TEAEs of special interest

Table 42. Grade 3-4 Treatment-emergent Adverse Events of Interest, Study 301

MedDRA Preferred term	E7389 (N=544) n (%)			Capecitabine (N=546) n (%)		
Subjects with any TEAE Grade ≥ 3						
CTCAE Grade	3	4	Total 3 + 4	3	4	Total 3 + 4
Neutropenia	134 (24.6)	115 (21.1)	249 (52.8)	23 (4.2)	4 (0.7)	27 (4.9)
Global peripheral neuropathy[a]	35 (6.4)	3 (0.6)	38 (7.0)	5 (0.9)	0	5 (0.9)
Fatigue/asthenia	32 (5.9)	1 (0.2)	33 (6.1)	31 (5.7)	1 (0.2)	32 (5.9)
Febrile neutropenia	8 (1.5)	3 (0.6)	11 (2.0)	2 (0.4)	3 (0.5)	5 (0.9)
Anthralgia/myalgia	4 (0.7)	1 (0.2)	5 (0.9)	2 (0.4)	0	2 (0.4)
Anthralgia/myalgia plus global peripheral neuropathy	1 (0.2)	0	1 (0.2)	0	0	0

Note: If a subject had multiple CTCAE grades for the same category of treatment-emergent adverse events of interest, the highest CTCAE grade was used for the subject.
CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, SMQ = standard MedDRA Queries, TEAE = treatment-emergent adverse event.
a: Defined as SMQ narrow and broad.

Source: Study 301 CSR, Table 41.

Neuropathy

Table 43. Treatment-emergent Peripheral Neuropathy in Eribulin-treated Subjects – Phase 2 / 3 Breast Cancer Trials

Category of Peripheral Neuropathy[a]	All Eribulin-treated Subjects in Study 301 (N=544) n (%)	All Eribulin-treated Subjects in Study 305 (N=503) n (%)	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503) n (%)
Total incidence of TEAEs	149 (27.4)	210 (41.7)	541 (36.0%)
Grade 3-4 TEAEs	38 (7.0)	45 (8.9)	116 (7.7)
Related TEAEs	128 (23.5)	182 (36.2)	472 (31.4)
Related, Grade 3-4 TEAEs	34 (6.3)	39 (7.8)	104 (6.9)
Nonfatal serious TEAEs	2 (0.4)	5 (1.0)	11 (0.7)
Related nonfatal serious TEAE	1 (0.2)	3 (0.6)	6 (0.4)
TEAEs with outcome of death	0	0	0
TEAEs that led to treatment discontinuation	9 (1.7)	24 (4.8)	50 (3.3)

MedDRA version 14.1.
Percentages are based on the number of safety subjects in each integrated analysis set.
MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standard MedDRA query; TEAE = treatment-emergent adverse event.
a: Per broad SMQ analysis, peripheral neuropathy includes allodynia, demyelinating polyneuropathy, hyperesthesia, neuropathy, neuropathy peripheral, painful response to normal stimuli, pallanesthesia, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Source: SCS, Table 33.

Table 44. Onset and Resolution of Treatment-Emergent Peripheral Neuropathy (by narrow SMQ)– Phase 2 / 3 Breast Cancer Trials

Category	All Eribulin-treated Subjects in Study 301 (N=544) n (%)	All Eribulin-treated Subjects in Study 305 (N=503) n (%)	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503) n (%)
Total no. of subjects with any treatment-emergent peripheral neuropathy[a]	116 (21.3)	174 (34.6)	446 (29.7)
Time to First Onset of Any Treatment-Emergent Peripheral Neuropathy, days[b]			
n	107	157	410
Mean (SD)	85.7 (96.29)	74.0 (67.19)	71.4 (75.30)
Median	63.0	62.0	56.0
Q1 - Q3	29.0 - 96.0	23.0 - 93.0	22.0 - 87.0
Min, max	1, 625	1, 407	1, 625
Time to Quickest Worsening of Treatment-Emergent Peripheral Neuropathy, days[b,c]			
n	20	26	66
Mean (SD)	58.5 (90.80)	28.3 (26.56)	40.7 (60.67)
Median	29.5	20.5	25.5
Q1 - Q3	13.0 - 59.0	11.0 - 36.0	11.0 - 43.0
Min, max	1, 412	1, 110	1, 412
Resolution of Treatment-Emergent Peripheral Neuropathy, n (%)[b,d,e]			
Subjects with ongoing peripheral neuropathy after last treatment[b]	81 (14.9)	118 (23.5)	307 (20.4)
Subjects with peripheral neuropathy resolved within 30 days after last dose[f]	17 (21.0)	28 (23.7)	85 (27.7)
Subjects died before peripheral neuropathy resolved within 30 days after last dose[f]	4 (4.9)	0	7 (2.3)
Subjects started new anticancer treatment before peripheral neuropathy resolved within 30 days after last dose[f]	16 (19.8)	5 (4.2)	57 (18.6)

Notes: Percentages are based on the number of safety subjects in each integrated analysis set.
Analysis of peripheral neuropathy based on narrow SMQ and includes the following preferred terms: neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, paraesthesia.
AE = adverse event; max = maximum; Medical Dictionary for Regulatory Activities; min = minimum; Q = quartile; SMQ = standard MedDRA query

a: Includes all episodes of treatment-emergent peripheral neuropathy that started during treatment or within 30 days after the last dose.
b: Includes only episodes of treatment-emergent peripheral neuropathy that started on or before the last dose date.
c: Includes only subjects who had multiple episodes of treatment-emergent peripheral neuropathy. "Time to worsening of treatment-emergent peripheral neuropathy" is defined as the shortest time to onset of any of the episodes.
d: Information on AEs was only collected for 30 days after each subject's last dose.
e: Resolution of peripheral neuropathy was determined by the investigator.
f: Percentages are based on the number of safety subjects with ongoing treatment-emergent peripheral neuropathy at the time of the last dose in each integrated analysis set.

Source: SCS, Table 35.

Table 45. Peripheral neuropathy ongoing after last treatment - Phase 2/3 breast cancer trials

Peripheral neuropathy	Study 301 (N=544)		Study 305 (N=503)		Pooled Phase 2/3 Breast Cancer Trials (N=1503)	
	Narrow SMQ	Broad SMQ	Narrow SMQ	Broad SMQ	Narrow SMQ	Broad SMQ
TEAEs n (%)	116 (21.3)	149 (27.4)	174 (34.6)	210 (41.7)	446 (29.7)	541 (36.0)
Ongoing after last treatment	81 (14.9)	98 (18.0)	118 (23.5)	146 (29.0)	307 (20.4)	370 (24.6)
Resolved within 30 days after last dose, n (% of pts w ongoing p.n.)	17 (21.0)	20 (20.4)	28 (23.7)	32 (21.9)	85 (27.7)	101 (27.3)
Died before peripheral neuropathy resolved within 30 days after last dose	4 (4.9)	4 (4.1)	0	0	7 (2.3)	7 (1.9)
Started new anticancer treatment before peripheral neuropathy resolved within 30 days after last dose	16 (19.8)	21 (21.4)	5 (4.2)	5 (3.4)	57 (18.6)	67 (18.1)
→ Not resolved within 30 days after last dose n (% of ongoing p.n. /% of all pts)	44 (54.3 / 8.1)	53 (54.1 / 9.7)	85 (72.0 / 16.9)	109 (74.7 / 21.7)	158 (51.46 /10.51)	195 (52.7 / 13.0)

Source: SCS, Table 13 and Table 35 (narrow SMQ), ISS tables p3, Table 2.26.4 (broad SMQ).

Based on Broad SMQ, 116 patients (7.7%) in the phase 2/3 breast cancer population experienced grade 3-4 peripheral neuropathy. 74 of these improved to grade 2 or lower, leaving 42 patients (2.8% of 1503) with remaining grade 3-4 neuropathy (Table 46).

Table 46. Improvement of Treatment-Emergent Grade 3-4 Peripheral Neuropathy Based on Broad SMQ – Safety Population Phase 2/3 Studies

	Completed Phase 2/3 Eribulin Studies (N=1503) (%)
Grade 3-4 peripheral neuropathy	116 (7.7)
Improvement of Grade 3-4 peripheral neuropathy [a]	74 (63.8)
Improved to Grade 2	17 (14.7)
Improved to Grade 1	20 (17.2)
Improved to Grade 0	37 (31.9)
Median time to improvement of Grade 3-4 peripheral neuropathy, weeks [b]	2.1
Grade 3-4 peripheral neuropathy resolved to Grade 1, 0 or baseline grade [a]	57 (49.1)
Median time to resolution to Grade 1, 0, or baseline (95%CI), weeks [c]	8.1 (5.9, 11.1)

Note: Patient was counted to best improvement.
SMQ = Standardised MedDRA Query
a: Percentage is based on patients with Grade 3/4 peripheral neuropathy (PN).
b: Improvement was defined as a decrease by one grade or more. Time to improvement was calculated from start of worst PN to start of PN with improvement. Grade 0 means PN stopped.
c: If PN was not resolved, time to resolution was censored at the earliest date of death, last dose + 30 days, last known alive date, or start of another anticancer therapy.

Arthralgia/Myalgia

Table 47. Treatment-emergent Arthralgia / Myalgia in Eribulin-treated Subjects – Phase 2 / 3 Breast Cancer Trials

Category of Arthralgia+Myalgia	All Eribulin-treated Subjects in Study 301 (N=544) n (%)	All Eribulin-treated Subjects in Study 305 (N=503) n (%)	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503) n (%)
Total incidence of TEAEs	66 (12.1)	110 (21.9)	293 (19.5)
Grade 3-4 TEAEs	5 (0.9)	2 (0.4)	16 (1.1)
Related TEAEs	22 (4.0)	54 (10.7)	146 (9.7)
Related, Grade 3-4 TEAEs	1 (0.2)	1 (0.2)	4 (0.3)
Nonfatal serious TEAEs	0	0	2 (0.1)
Related nonfatal serious TEAEs	0	0	0
TEAEs with outcome of death	0	0	0
TEAEs led to treatment discontinuation	0	0	2 (0.1)

MedDRA version 14.1.
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Source: SCS, Table 37.

Cardiac Events

Table 48. Treatment-emergent Cardiac Events in Eribulin-treated Subjects – Phase 2 / 3 Breast Cancer Trials

Category of Cardiac Events	All Eribulin-treated Subjects in Study 301 (N=544) n (%)	All Eribulin-treated Subjects in Study 305 (N=503) n (%)	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503) n (%)
Total incidence of TEAEs	34 (6.3)	34 (6.8)	103 (6.9)
Grade 3-4 TEAEs	5 (0.9)	3 (0.6)	12 (0.8)
Related TEAEs	17 (3.1)	8 (1.6)	41 (2.7)
Related, Grade 3-4 TEAEs	4 (0.7)	1 (0.2)	6 (0.4)
Nonfatal serious TEAEs	5 (0.9)	3 (0.6)	12 (0.8)
Related nonfatal serious TEAEs	4 (0.7)	0	7 (0.5)
TEAEs with outcome of death	2 (0.4)	1 (0.2)	4 (0.3)
TEAEs led to treatment discontinuation	3 (0.6)	0	4 (0.3)

MedDRA version 14.1.
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Source: SCS, Table 38.

QT prolongation

There were no events of torsades de pointes reported for eribulin-treated subjects in the Phase 2/3 breast cancer trials. However, QT prolongation was reported as a non-serious TEAE in two eribulin-treated subjects in Study 301. Both had hypokalemia as potential contributing factors. Two capecitabine-treated subjects also had QT prolongation. None led to treatment discontinuation. (SCS, p. 102, Response Q26)

In addition there were 5 of the eribulin-treated patients (0.9% of Study 301 safety population) who had > 60 ms prolongation of QTc from baseline and in two of these patients, values over 500 ms were reported according to QTcB, one of the two also reached 500 ms by QTcF. In one of these 5 cases hypokalemia was reported (in combination with infection and brain metastases), in another vomiting (potential cause of electrolyte imbalance), in a third no electrolyte imbalance was present.

Individual case reports were scrutinised and a more detailed tabulation of QT events was considered inconspicuous (see below). Thus there are no outstanding concerns from this perspective.

Table 49. ECG QT prolongation events in Study 301

ECG Parameter	Visit	Treatment Groups	
		E7389 (N=544) n (%)	Capecitabine (N=546) n (%)
QTc – Fridericia (ms)			
Subjects with baseline	Baseline	532	528
Value of >450 ms		19 (3.6)	10 (1.9)
Value of >480 ms		2 (0.4)	1 (0.2)
Value of >500 ms		2 (0.4)	0
Subjects with baseline and postbaseline data	Cycle 2	426	410
Increase of >30 ms		48 (11.3)	27 (6.6)
Increase of >60 ms		4 (0.9)	3 (0.7)
Value of >450 ms		19 (4.5)	11 (2.7)
Value of >480 ms		0	1 (0.2)
Value of >500 ms		0	1 (0.2)
Subjects with baseline and postbaseline data	End of treatment	371	350
Increase of >30 ms		30 (8.1)	32 (9.1)
Increase of >60 ms		1 (0.3)	1 (0.3)
Value of >450 ms		13 (3.5)	5 (1.4)
Value of >480 ms		4 (1.1)	0
Value of >500 ms		1 (0.3)	0
Subjects with baseline and postbaseline data	Overall	478	467
Increase of >30 ms		67 (14.0)	50 (10.7)
Increase of >60 ms		5 (1.0)	4 (0.9)
Value of >450 ms		26 (5.4)	16 (3.4)
Value of >480 ms		4 (0.8)	1 (0.2)
Value of >500 ms		1 (0.2)	1 (0.2)

Subjects are counted in each applicable category
Percentages are based on the number of subjects with non-missing baseline and postbaseline data.

Asthenia / Fatigue

Table 50. Adverse Event Profile for Treatment-emergent Asthenia / Fatigue in Eribulin-treated Subjects – Phase 2 / 3 Breast Cancer Trials

Category of Asthenia+Fatigue	All Eribulin-treated Subjects in Study 301 (N=544) n (%)	All Eribulin-treated Subjects in Study 305 (N=503) n (%)	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503) n (%)
Total incidence of TEAEs	165 (30.3)	269 (53.5)	723 (48.1)
Grade 3-4 TEAEs	33 (6.1)	51 (10.1)	123 (8.2)
Related TEAEs	127 (23.3)	229 (45.5)	622 (41.4)
Related Grade 3-4 TEAEs	24 (4.4)	38 (7.6)	97 (6.5)
Nonfatal serious TEAEs	6 (1.1)	6 (1.2)	16 (1.1)
Related nonfatal serious TEAEs	3 (0.6)	3 (0.6)	8 (0.5)
TEAEs with outcome of death	0	0	0
TEAEs that led to treatment discontinuation	2 (0.4)	9 (1.8)	12 (0.8)

MedDRA version 14.1.
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Source: SCS, Table 36.

Serious adverse event / deaths / other significant events

Serious adverse events

Table 51. Treatment-emergent Serious Adverse Events Experienced by Two of More Subjects in any Treatment Group, Study 301

MedDRA SOC Preferred term	E7389 (N=544) n (%)		Capecitabine (N=546) n (%)	
	Total	Related	Total	Related
No. (%) of subjects with ≥1 SAE	95 (17.5)	42 (7.7)	115 (21.1)	44 (8.1)
Blood and lymphatic system disorders	**21 (3.9)**	**18 (3.3)**	**6 (1.1)**	**6 (1.1)**
Neutropenia	10 (1.8)	10 (1.8)	1 (0.2)	1 (0.2)
Febrile neutropenia	7 (1.3)	6 (1.1)	4 (0.7)	4 (0.7)
Leukopenia	4 (0.7)	4 (0.7)	0	0
Anaemia	3 (0.6)	2 (0.4)	0	0
Cardiac disorders	**6 (1.1)**	**4 (0.7)**	**10 (1.8)**	**1 (0.2)**
Cardiac failure	0	0	2 (0.4)	0
Gastrointestinal disorders	**9 (1.7)**	**3 (0.6)**	**26 (4.8)**	**22 (4.0)**
Vomiting	2 (0.4)	0	9 (1.6)	6 (1.1)
Abdominal pain	2 (0.4)	0	1 (0.2)	1 (0.2)
Diarrhoea	1 (0.2)	1 (0.2)	15 (2.7)	14 (2.6)
Nausea	1 (0.2)	0	7 (1.3)	7 (1.3)
Dysphagia	0	0	2 (0.4)	1 (0.2)
General disorders and administration site conditions	**15 (2.8)**	**8 (1.5)**	**26 (4.8)**	**6 (1.1)**
Pyrexia	3 (0.6)	1 (0.2)	5 (0.9)	3 (0.5)
Asthenia	3 (0.6)	1 (0.2)	4 (0.7)	0
Fatigue	3 (0.6)	2 (0.4)	4 (0.7)	1 (0.2)
Death	1 (0.2)	1 (0.2)	4 (0.7)	0
General physical health deterioration	1 (0.2)	1 (0.2)	3 (0.5)	0
Multi-organ failure	1 (0.2)	0	2 (0.4)	0
Mucosal inflammation	0	0	2 (0.4)	2 (0.4)
Hepatobiliary disorders	**4 (0.7)**	**3 (0.6)**	**1 (0.2)**	**0**
Hepatitis toxic	2 (0.4)	2 (0.4)	0	0
Infections and infestations	**12 (2.2)**	**4 (0.7)**	**15 (2.7)**	**6 (1.1)**
Pneumonia	4 (0.7)	1 (0.2)	4 (0.7)	2 (0.4)
Sepsis	2 (0.4)	1 (0.2)	4 (0.7)	3 (0.5)
Bronchitis	0	0	3 (0.5)	0
Cellulitis	0	0	2 (0.4)	1 (0.2)

Table continued on next page

Injury, poisoning, and procedural complications	**6 (1.1)**	**1 (0.2)**	**5 (0.9)**	**1 (0.2)**
Femur fracture	1 (0.2)	0	2 (0.4)	0
Metabolism and nutrition disorders	**4 (0.7)**	**2 (0.4)**	**15 (2.7)**	**7 (1.3)**
Dehydration	1 (0.2)	1 (0.2)	9 (1.6)	4 (0.7)
Hyperglycaemia	1 (0.2)	0	2 (0.4)	0
Musculoskeletal and connective tissue disorders	4 (0.7)	1 (0.2)	2 (0.4)	0
Back pain	2 (0.4)	0	0	0
Neoplasms benign, malignant and unspecified	**10 (1.8)**	**0**	**12 (2.2)**	**0**
Neoplasm malignant	7 (1.3)	0	2 (0.4)	0
Oncologic complication	0	0	2 (0.4)	0
Tumour pain	0	0	2 (0.4)	0
Nervous system disorders	**12 (2.2)**	**3 (0.6)**	**19 (3.5)**	**1 (0.2)**
Headache	2 (0.4)	1 (0.2)	4 (0.7)	0
Cerebrovascular accident	2 (0.4)	1 (0.2)	2 (0.4)	0
Spinal cord compression	2 (0.4)	0	2 (0.4)	0
Convulsion	1 (0.2)	1 (0.2)	2 (0.4)	0
Depressed level of consciousness	0	0	2 (0.4)	0
Psychiatric disorders	**4 (0.7)**	**2 (0.4)**	**1 (0.2)**	**0**
Mental status changes	2 (0.4)	0	1 (0.2)	0
Confusional state	2 (0.4)	2 (0.4)	0	0
Respiratory, thoracic and mediastinal disorders	**22 (4.0)**	**3 (0.6)**	**28 (5.1)**	**4 (0.7)**
Dyspnoea	13 (2.4)	3 (0.6)	17 (3.1)	2 (0.4)
Respiratory failure	5 (0.9)	0	7 (1.3)	0
Pleural effusion	2 (0.4)	0	2 (0.4)	0
Pulmonary embolism	1 (0.2)	0	3 (0.5)	1 (0.2)
Hydrothorax	1 (0.2)	0	2 (0.4)	0
Respiratory distress	0	0	2 (0.4)	0
Skin and subcutaneous tissue disorders	**0**	**0**	**2 (0.4)**	2 (0.4)
Palmar-plantar erythrodysaesthesia syndrome	0	0	2 (0.4)	2 (0.4)
Vascular disorders	**4 (0.7)**	**0**	**7 (1.3)**	**2 (0.4)**
Deep vein thrombosis	2 (0.4)	0	3 (0.5)	1 (0.2)

MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event, SOC = system organ class.

Source: Study 301 CSR, Table 39.

Deaths

BCP

Overall, 67 eribulin-treated subjects (4.5%) in the Phase 2/3 breast cancer trials had a TEAE associated with an outcome of death. That is, these TEAEs were ongoing at the time of the death and may not have been the primary cause of death. The only TEAEs associated with an outcome of death in more than two subjects were neoplasm malignant (n=10, 0.7%), dyspnoea (9, 0.6%), respiratory failure (8, 0.5%), metastases to meninges (3, 0.2%), disease progression (3, 0.2%), and sepsis (3, 0.2%).

Study 301

In Study 301, 26 of the 544 subjects (4.8%) in the eribulin group and 36 of the 546 subjects (6.6%) in the capecitabine group died during the treatment period or within 30 days of last dose of study treatment.

Eribulin arm

Nine deaths in the eribulin group were associated with an AE (1.7%). Fifteen deaths (2.8%) were attributed to disease progression. For two subjects (0.4%) the primary cause of death was listed as "unknown."

In the in the eribulin group, there were 11 TEAEs reported with an outcome of death, 5 (possibly) related (R) and 6 not related (N). In two cases the investigator's final judgement on cause of death was another than the reported TEAE ("unknown" and "disease progression", respectively, shown with arrows in the summary below):

2 Sepsis (1 R, 1 N), 1 Renal failure (R), 2 Respiratory failure (2 N), 1 Dyspnoea (N), 1 Stroke (N), 1 Toxic hepatitis (R), 1 Multiple organ failure (N), 1 pericardial effusion (R) -> Disease progression,1 Sudden death (R) -> Unknown.

Capecitabine arm

In the capecitabine group, 13 deaths were associated with an AE (2.4%), 22 (4.0%) were due to disease progression. For 1 subject (0.2%), the primary cause of death was listed as "unknown."

In the in the capecitabine group, there were 14 TEAEs reported with an outcome of death, 4 (possibly) related (R) and 10 not related (N). In one case, the investigator's final judgement on cause of death was "unknown".
1 Hypercalcaemia (N), 1 Cardiac and respiratory arrest (N), 1 Respiratory failure (N), 1 Pneumonia (R), 1 Intracranial hypertension (N), 1 Haemorrhagic shock (N), 1 Cardiogenic shock(R), 1 Respiratory distress (N) -> Unknown, 1 Sepsis (R), 1 Pancytopenia (R), 1 Sudden death (N), 1 Cerebellar infarction (N), 1 Multiple organ failure (N), 1 Stroke (N).
TEAES with fatal outcome in Study 301 of particular interest (CSR, Table 14.3.2.1.2.1):

- Toxic hepatitis: 1 in the eribulin arm - 0 in the capecitabine arm.
- Pancytopenia: 0 in the eribulin arm – 1 in the capecitabine arm.
- Cardiac disorders SOC (all terms): 2 (0.4%) in the eribulin arm - 4 (0.7%) in the capecitabine arm
- "Infections…" SOC (all terms): 2 (0.4) (=2 sepsis) in the eribulin arm - 2 (0.4) (= sepsis; pneumonia) in the capecitabine arm
- Nervous system disorders SOC (all terms): 1 (0.2) in the eribulin arm - 6 (1.1) in the capecitabine arm.

Treatment-related deaths

There was no difference between Studies 301 and 305 in the overall incidence of deaths due to TEAEs reported as treatment related (n=5 [0.9%] vs. 5 [1.0%] for Studies 301 and 305, respectively). In Study 301, the five deaths reported as related to eribulin by the investigator included pericardial effusion, sudden death, hepatic toxicity, sepsis, and renal failure. In Study 305, the five deaths reported as related to eribulin included dyspnoea, febrile neutropenia, bronchopneumonia, and lung infection.

In the capecitabine group in Study 301, four deaths (0.7%) were considered to be treatment related by the investigator, and included pneumonia, cardiogenic shock, sepsis, and pancytopenia in one subject each. (SCS p. 77)

Discontinuation due to adverse events

Table 52. Primary reasons for discontinuation from Study 301

Discontinued study, n (%)	549 (99.1)	543 (99.1)	1092 (99.1)
Primary reason for discontinuation, n (%)			
Progression of disease[c]	409 (73.8)	405 (73.9)	814 (73.9)
Adverse event[d]	45 (8.1)	59 (10.8)	104 (9.4)
Subject choice[e]	34 (6.1)	27 (4.9)	61 (5.5)
Clinical progression	27 (4.9)	24 (4.4)	51 (4.6)
Physician's decision	15 (2.7)	14 (2.6)	29 (2.6)
Subject withdrew consent	8 (1.4)	5 (0.9)	13 (1.2)
Other	5 (0.9)	6 (1.1)	11 (1.0)
Entry criteria not met	4 (0.7)	1 (0.2)	5 (0.5)
Lost to follow-up	1 (0.2)	2 (0.4)	3 (0.3)
Death	1 (0.2)	0 (0.0)	1 (0.1)

c: Progressive disease assessed using Response Evaluation Criteria in Solid Tumours (RECIST).

d: Four subjects discontinued due to an AE, although the AE leading to discontinuation was recorded more than 30 days after the last dose of study drug.

Source: Study 301 CSR, Table 7.

Note: According to footnote of CSR, Table 7 (Table 52), four subjects discontinued due to an AE, although the AE leading to discontinuation was recorded more than 30 days after the last dose of study drug. When counting these 4 cases, the cause for discontinuation from Study 301 was an adverse event in 8.1% of the eribulin-treated patients and 10.8% of the capecitabine-treated patients. In the CSR table 40 (

Table **54**), however, these patients do not seem to be included, and the resultant frequencies are 7.9% vs. 10.4%, congruent with SCS table 26 (

Table **53**).

Table 53. TEAEs That Led To Discontinuation Of Eribulin in Two or More Subjects by SOC and PT – Phase 2 / 3 Breast Cancer Trials

MedDRA System Organ Class Preferred Term	All Eribulin-treated Subjects in Study 301 (N=544) n (%)	All Eribulin-treated Subjects in Study 305 (N=503) n (%)	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503) n (%)
Subjects with any TEAE leading to discontinuation of treatment	43 (7.9)	68 (13.5)	157 (10.4)
Blood and Lymphatic System Disorders	**9 (1.7)**	**4 (0.8)**	**16 (1.1)**
Neutropenia	9 (1.7)	3 (0.6)	13 (0.9)
Febrile neutropenia	0	0	2 (0.1)
Gastrointestinal Disorders	**3 (0.6)**	**6 (1.2)**	**10 (0.7)**
Ascites	0	2 (0.4)	2 (0.1)
General Disorders and Administration Site Conditions	**3 (0.6)**	**10 (2.0)**	**17 (1.1)**
Asthenia + Fatigue	2 (0.4)	9 (1.8)	12 (0.8)
Asthenia	2 (0.4)	4 (0.8)	7 (0.5)
Fatigue	0	5 (1.0)	5 (0.3)
Pain	0	1 (0.2)	2 (0.1)
Infections and Infestations	**2 (0.4)**	**5 (1.0)**	**9 (0.6)**
Pneumonia	1 (0.2)	2 (0.4)	3 (0.2)
Investigations	**2 (0.4)**	**8 (1.6)**	**10 (0.7)**
Weight decreased	0	3 (0.6)	3 (0.2)
ALT increased	1 (0.2)	1 (0.2)	2 (0.1)
Metabolism and Nutrition disorders	**1 (0.2)**	**2 (0.4)**	**4 (0.3)**
Hyperglycemia	1 (0.2)	1 (0.2)	2 (0.1)
Musculoskeletal and Connective Tissue disorders	**1 (0.2)**	**2 (0.4)**	**10 (0.7)**
Arthralgia + myalgia	0	0	2 (0.1)
Muscular weakness	0	0	2 (0.1)
Pathological fracture	1 (0.2)	0	2 (0.1)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**1 (0.2)**	**3 (0.6)**	**12 (0.8)**
Neoplasm malignant	1 (0.2)	0	3 (0.2)
Metastases to meninges	0	1 (0.2)	2 (0.1)
Nervous System disorders	**12 (2.2)**	**29 (5.8)**	**61 (4.1)**
Peripheral neuropathy, broad SMQ	9 (1.7)	24 (4.8)	50 (3.3)
Peripheral neuropathy, narrow SMQ	9 (1.7)	24 (4.8)	48 (3.2)
Peripheral sensory neuropathy	5 (0.9)	11 (2.2)	18 (1.2)
Neuropathy peripheral	0	8 (1.6)	17 (1.1)
Peripheral motor neuropathy	1 (0.2)	6 (1.2)	9 (0.6)
Polyneuropathy	2 (0.4)	1 (0.2)	4 (0.3)
Paraesthesia	0	2 (0.4)	3 (0.2)
Cerebrovascular accident	1 (0.2)	0	2 (0.1)
Peripheral sensorimotor neuropathy	1 (0.2)	0	2 (0.1)
Respiratory, Thoracic, Mediastinal disorders	**4 (0.7)**	**5 (1.0)**	**12 (0.8)**
Pleural effusion	0	4 (0.8)	5 (0.3)
Dyspnea	2 (0.4)	1 (0.2)	4 (0.3)
Respiratory failure	2 (0.4)	0	3 (0.2)

Table 54. TEAEs in Study 301 Leading to Discontinuation of Study Drug by SOC and PT

MedDRA System Organ Class / Preferred Term	Treatment Groups	
	E7389 (N=544) n (%)	Capecitabine (N=546) n (%)
Subjects with any TEAE leading to discontinuation of study drug	**43 (7.9)**	**57 (10.4)**
Blood and lymphatic system disorders	**9 (1.7)**	**6 (1.1)**
Neutropenia	9 (1.7)	1 (0.2)
Leukopenia	1 (0.2)	0
Thrombocytopenia	0	3 (0.5)
Eosinophilia	0	1 (0.2)
Febrile neutropenia	0	1 (0.2)
Pancytopenia	0	1 (0.2)
Cardiac disorders	**3 (0.6)**	**2 (0.4)**
Myocardial infarction	1 (0.2)	1 (0.2)
Coronary artery insufficiency	1 (0.2)	0
Left ventricular dysfunction	1 (0.2)	0
Cardiac failure	0	1 (0.2)
Gastrointestinal disorders	**3 (0.6)**	**6 (1.1)**
Stomatitis	1 (0.2)	1 (0.2)
Haematemesis	1 (0.2)	0
Intestinal ischaemia	1 (0.2)	0
Diarrhoea	0	2 (0.4)
Dysphagia	0	1 (0.2)
Mouth Haemorrhage	0	1 (0.2)
Proctalgia	0	1 (0.2)
Vomiting	0	1 (0.2)
General disorders and administration site conditions	**3 (0.6)**	**10 (1.8)**
Asthenia	2 (0.4)	2 (0.4)
Multi-organ failure	1 (0.2)	2 (0.4)
Fatigue	0	2 (0.4)
Mucosal inflammation	0	2 (0.4)
Death	0	2 (0.4)
General physical health deterioration	0	1 (0.2)

Continued on next page

Hepatobiliary disorders	**4 (0.7)**	**4 (0.7)**
Hepatoxicity	1 (0.2)	1 (0.2)
Hepatic failure	1 (0.2)	0
Hepatic function abnormal	1 (0.2)	0
Hepatitis toxic	1 (0.2)	0
Hyperbilirubinaemia	0	2 (0.4)
Jaundice	0	1 (0.2)
Immune system disorders	**1 (0.2)**	**1 (0.2)**
Sarcoidosis	1 (0.2)	0
Hypersensitivity	0	1 (0.2)
Injury, poisoning and procedural complications	**0**	**3 (0.5)**
Femoral neck fracture	0	1 (0.2)
Femur fracture	0	1 (0.2)
Lower limb fracture	0	1 (0.2)
Investigations	**2 (0.4)**	**3 (0.5)**
Aspartate aminotransferase increased	1 (0.2)	2 (0.4)
Alanine aminotransferase increased	1 (0.2)	0
Gamma-glutamyltransferase increased	1 (0.2)	0
Hepatic enzyme increased	0	1 (0.2)
Metabolism and nutritional disorders	**1 (0.2)**	**4 (0.7)**
Hyperglycaemia	1 (0.2)	1 (0.2)
Hypoalbuminaemia	0	2 (0.4)
Decreased appetite	0	1 (0.2)
Hypercalcaemia	0	1 (0.2)
Hypocalcaemia	0	1 (0.2)
Hypokalaemia	0	1 (0.2)
Hypoproteinaemia	0	1 (0.2)
Musculoskeletal and connective tissue disorders	**1 (0.2)**	**1 (0.2)**
Pathological fracture	1 (0.2)	0
Muscular weakness	0	1 (0.2)

Continued on next page

Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1 (0.2)**	**1 (0.2)**
Neoplasm malignant	1 (0.2)	0
Rectal cancer	0	1 (0.2)
Nervous system disorders	**12 (2.2)**	**7 (1.3)**
Peripheral sensory neuropathy	5 (0.9)	1 (0.2)
Polyneuropathy	2 (0.4)	0
Cerebrovascular accident	1 (0.2)	2 (0.4)
Peripheral motor neuropathy	1 (0.2)	1 (0.2)
Peripheral sensorimotor neuropathy	1 (0.2)	0
Syncope	1 (0.2)	0
Transient ischaemic attack	1 (0.2)	0
Aphasia	0	1 (0.2)
Cerebellar infarction	0	1 (0.2)
Convulsion	0	1 (0.2)
Depressed level of consciousness	0	1 (0.2)
Paraesthesia	0	1 (0.2)
Psychiatric disorders	**0**	**1 (0.2)**
Bradyphrenia	0	1 (0.2)
Renal and urinary disorders	**1 (0.2)**	**0**
Renal failure	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	**4 (0.7)**	**10 (1.8)**
Dyspnoea	2 (0.4)	6 (1.1)
Respiratory failure	2 (0.4)	4 (0.7)
Pulmonary embolism	0	1 (0.2)
Respiratory distress	0	1 (0.2)
Skin and subcutaneous tissue disorders	**1 (0.2)**	**13 (2.4)**
Urticaria	1 (0.2)	0
Palmar-plantar erythrodysaesthesia syndrome	0	12 (2.2)
Rash	0	2 (0.4)
Nail disorder	0	1 (0.2)
Skin exfoliation	0	1 (0.2)
Vascular disorders	**0**	**4 (0.7)**
Deep vein thrombosis	0	3 (0.5)
Shock haemorrhagic	0	1 (0.2)

MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event.
SOC = System Order Class, PT = Preferred Term

Source: Study 301 CSR, Table 40.

Laboratory findings

Haematology

Shifts from CTC toxicity grade 0-1 at Baseline to grade 3-4 during treatment were most frequently recorded for Absolute neutrophil count (ANC). In the BCP, 60% of eribulin-treated subjects had a shift in ANC value from grade 0-1 at Baseline to Grade 3-4 sometime during treatment, compared to 58% of eribulin-treated subjects in Study 301 and 56% in Study 305. Overall, the frequencies of shifts in haematology laboratory tests in Study 301 were consistent with the previously known safety profile (or slightly improved). As before, haemoglobin and platelets rarely reached toxicity grade 3 or 4 (Table 55).

Table 55. Haematology laboratory values

	All Eribulin-treated Subjects in Study 301 (N=544) n (%) [a]		All Eribulin-treated Subjects in Study 305 (N=503) n (%) [b]		All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503) n (%) [a]	
Laboratory Test	Worst CTC Grade During Treatment:					
Baseline Grade	3	4	3	4	3	4
Absolute lymphocyte count (x 10^9/L)						
0	28 (5.1)	6 (1.1)	17 (3.4)	3 (0.6)	56 (3.7)	12 (0.8)
1	7 (1.3)	0 (0)	24 (4.8)	4 (0.8)	49 (3.3)	5 (0.3)
Absolute neutrophil count (x 10^9/L)						
0	149 (27.4)	152 (27.9)	138 (27.4)	135 (26.8)	399 (26.5)	468 (31.1)
1	7 (1.3)	7 (1.3)	3 (0.6)	7 (1.4)	16 (1.1)	19 (1.3)
Hemoglobin (g/L)						
0	3 (0.6)	0 (0)	2 (0.4)	1 (0.2)	7 (0.5)	2 (0.1)
1	5 (0.9)	0 (0)	4 (0.8)	1 (0.2)	15 (1.0)	2 (0.1)
Leukocyte count (x 10^9/L)						
0	124 (22.8)	14 (2.6)	138 (27.4)	19 (3.8)	418 (27.8)	55 (3.7)
1	20 (3.7)	1 (0.2)	18 (3.6)	4 (0.8)	68 (4.5)	8 (0.5)
Platelet count (x 10^9/L)						
0	1 (0.2)	0 (0)	4 (0.8)	2 (0.4)	7 (0.5)	2 (0.1)
1	1 (0.2)	0 (0)	1 (0.2)	0 (0)	4 (0.3)	1 (0.1)

Percentages are based on the total number of subjects with non-missing lab measurements in each cycle for each integrated analysis set.
CTC grade is based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).
CTC Grade 0 = Within normal range or abnormal in a direction in which CTC grade is not defined.
a: Assessed through Cycle 65. b: Assessed through Cycle 23.
Source: SCS, Table 42.

Clinical chemistry

Table 56.Shifts in Serum Chemistry Laboratory Values from CTC Grade 0 or 1 at Baseline to Worst Overall Grade of 3 or 4 During Treatment – Phase 2/3 Breast Cancer Trials

	All Eribulin-treated Subjects in Study 301 (N=544)		All Eribulin-treated Subjects in Study 305 (N=503)		All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503)	
Laboratory Test	Worst Grade During Treatment, n (%):					
Baseline Grade	3	4	3	4	3	4
Alkaline phosphatase						
0	2 (0.4)	0	1 (0.2)	0	4 (0.3)	0
1	3 (0.6)	0	7 (1.4)	0	18 (1.2)	0
ALT						
0	18 (3.4)	0	3 (0.6)	0	24 (1.6)	0
1	14 (2.7)	0	8 (1.6)	0	30 (2.0)	0
AST						
0	5 (1.0)	0	3 (0.6)	0	11 (0.7)	0
1	11 (2.1)	0	6 (1.2)	0	23 (1.6)	0
Albumin						
0	1 (0.2)	0	1 (0.2)	0	3 (0.2)	0
1	0	0	1 (0.2)	0	1 (0.1)	0
Total bilirubin						
0	3 (0.6)	0	4 (0.8)	0	9 (0.6)	0
1	0	0	1 (0.2)	0	1 (0.1)	0
Creatinine						
0	0	0	2 (0.4)	3 (0.6)	2 (0.1)	3 (0.2)
1	0	0	0	0	0	0
Phosphate						
0	11 (2.1)	1 (0.2)	22 (4.8)	5 (1.1)	42 (3.0)	6 (0.4)
1	0	0	0	0	0	0
Calcium high						
0	4 (0.7)	4 (0.7)	2 (0.4)	8 (1.6)	7 (0.5)	13 (0.9)
1	0	0	0	0	2 (0.1)	1 (0.1)
Calcium low						
0	7 (1.3)	3 (0.6)	6 (1.2)	5 (1.0)	16 (1.1)	8 (0.5)
1	1 (0.2)	0	1 (0.2)	0	2 (0.1)	0
Potassium high						
0	6 (1.1)	2 (0.4)	2 (0.4)	2 (0.4)	10 (0.7)	5 (0.3)
1	2 (0.4)	1 (0.2)	0	1 (0.2)	2 (0.1)	2 (0.1)
Potassium low						
0	18 (3.3)	4 (0.7)	15 (3.0)	3 (0.6)	45 (3.0)	8 (0.5)
1	1 (0.2)	1 (0.2)	5 (1.0)	0	12 (0.8)	1 (0.1)
Magnesium high						
0	31 (5.9)	0	14 (3.1)	1 (0.2)	47 (3.6)	2 (0.2)
1	3 (0.6)	0	2 (0.4)	0	5 (0.4)	0

Magnesium low						
0	1 (0.2)	1 (0.2)	3 (0.7)	1 (0.2)	4 (0.3)	2 (0.2)
1	1 (0.2)	0	1 (0.2)	0	2 (0.2)	0
Sodium high						
0	6 (1.1)	3 (0.6)	4 (0.8)	11 (2.2)	10 (0.7)	14 (0.9)
1	1 (0.2)	0	6 (1.2)	2 (0.4)	1 (0.1)	0
Sodium low						
0	9 (1.7)	2 (0.4)	11 (2.2)	12 (2.4)	27 (1.8)	14 (0.9)
1	5 (0.9)	0	6 (1.2)	2 (0.4)	16 (1.1)	2 (0.1)

Percentages are based on the total number of subjects with non-missing lab measurements in each cycle for each integrated analysis set.
CTC grade is based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).
CTC Grade 0 = Within normal range or abnormal in a direction in which CTC grade is not defined.
a: Assessed through Cycle 65.
b: Assessed through Cycle 23.
Source: SCS, Table 46.

Liver function tests

Although not noted as clinically significant, increases from baseline in ALT and AST assessed as CTCAE Grade 2 were frequently observed during the early treatment cycles (Cycles 1 and 2). No concurrent change from baseline was observed for total bilirubin, LDH, or alkaline phosphatase for subjects in the eribulin group.

Liver toxicity grade ≥ 3was reported as a TEAE 1.1% of eribulin-treated patients in Study 301. While 3 patients fulfilled the laboratory criteria for Hy's, none of them fulfilled the clinical criteria of absence of other plausible explanation, in these cases in the form of progressing liver metastases or cholestasis.

In the eribulin arm of Study 301, 104 (21%) of the 502 patients with baseline ALT grade 0 or 1 had shifts to grade 2 or 3 post baseline, compared with 51 (10%) of 500 patients in the capecitabine arm. On the other hand, more patients in the capecitabine arm (n=119, all of whom had baseline grade 0-1 bilirubin) had bilirubin elevation to grade 2 (Hy's law cut-off), compared with 26 patients (also all with baseline grade 0-1) in the eribulin arm.

Grade 3 ALT elevation

Of the 37 eribulin-treated patients in Study 301 who had ALT elevation grade 3, most hade elevation to maximum 5-6 x upper limit of normal (ULN). Three patients had elevation to 7 x ULN, one each to 8, 10 and 12 x ULN, respectively, and two to 16 x ULN. A majority of these patients had their highest ALT elevation in cycles 1 (n=14) and 2 (n=9). Liver metastases were present in 22 of the 37 cases, no liver metastases in 13, and for 2 of the patients no clinical data were provided. Of the 13 patients without liver metastases, all but one had elevated LFTs reported from baseline. Liver toxicity was reported in 5 of the 37 cases; all five had some baseline elevation of LFTs, three had liver metastasis and a fourth had a history of cholecystitis. Thus, due to the presence of confounding factors in virtually all cases, no firm conclusions can be drawn on the relationship between eribulin and these grade 3 ALT elevations.

The pattern of frequent early ALT increases of little or no clinical consequence returning to normal in later cycles is acknowledged. This is sometimes referred to as "tolerance" and in the absence of bilirubin elevations is believed to have little or no potential for serious toxicity (The Clinical White Paper on DILI).

Safety in special populations

Age

In the Phase 2/3 breast cancer trials, 209 eribulin-treated subjects were >65 to 75 years of age and 24 subjects were >75 years of age. In the Phase 2/3 breast cancer trials, there were no notable differences in the overall AE profile of eribulin by age group.

Among eribulin-treated subjects in the Phase 2/3 breast cancer trials, there appeared to be no effect of age on any treatment-emergent abnormal hematology or chemistry laboratory values or on the incidence of Grade 3-4 laboratory abnormalities at Baseline and during treatment. (SCS p 124,126).

Race

No firm conclusions can be drawn regarding the safety of eribulin by racial category, given the small number of black and Asian subjects in the Safety population.

Japanese subjects enrolled in Study 221/224 had a very high rate of Grade 3-4 neutropenia (Grade 4 neutropenia occurred in 70.4% of subjects), not consistent with the results for any other trial in this submission. The MAH has found no biological basis for the high incidence of Grade 3-4 neutropenia in Study 221/224. The data in non-Japanese Asian patients are between Japanese and Western data, although the number of such patients is presently small.

Interim results of a post-marketing surveillance study in Japanese patients with MBC, based on 836 of in total 968 patients, shows an incidence of Grade 3-4 neutropenia (486 patients [58.1%]) and febrile neutropenia (56 patients [6.7%]) comparable to that observed in non-Japanese patients. This suggests that the finding in Study 221/224 may not be representative of the clinical reality.

Baseline Body Surface Area (BSA)

The overall AE profile of eribulin is presented for the Safety populations by BSA (<1.50, 1.50-<1.70, 1.70-2.0, >2.0-2.2, >2.2 m^2). Among eribulin-treated subjects in the Phase 2/3 breast cancer trials, there was no notable pattern in the overall TEAE incidence with increasing BSA. There did appear to be higher incidences of hematologic TEAEs in subjects with lower BSA (total, severe and related TEAEs). This finding appears to be driven by the fact that 59 of the 81 subjects in the Japanese Studies 221/224 were included in the lowest BSA category. Japanese subjects enrolled in Study 221/224 had a very high rate of Grade 3-4 neutropenia (Grade 4 neutropenia occurred in 70.4% of subjects), not consistent with the results for any other trial in this submission. When subjects enrolled in Studies 221/224 were removed from the analysis, there did not appear to be differences in overall AE profile across BSA categories. However, no firm conclusions can be drawn, given the small number of subjects in some of the categories.

In conclusion, when the Japanese subjects in Study 221/224 (with the unusually high rate of Grade 3-4 neutropenia) were removed from the analysis, Baseline Body Surface Area (BSA) did not affect TEAE frequencies.

Liver impairment

Hepatic impairment increases exposure to eribulin. According to population PK analyses, decreased clearance is associated with decreased albumin, increased bilirubin, and increased alkaline phosphatase. Compared with subjects with normal hepatic function, exposure to eribulin increased 1.75-fold and 2.79 fold in subjects with mild and moderate hepatic impairment, respectively.

Overall, there was an increase in the incidence of severe and serious TEAEs with increasing baseline total bilirubin, ALT, and AST levels. There appeared to be a trend towards a higher incidence of total TEAEs, severe TEAEs (Grade ≥3), serious TEAEs and deaths due to a TEAE in subjects with a low baseline albumin level. In general, the overall AE profile of eribulin in subjects with hepatic impairment at Baseline was similar to those without hepatic impairment except that subjects with hepatic impairment at Baseline had a slightly higher incidence of deaths (7.4% vs. 4.1%).

There was an approximately 8% increase in peripheral neuropathy (by narrow and broad SMQ) for events of any grade, and around 6% increase in grade 3-4 events, in patients with ALT or AST elevation to > 3 x ULN, or Bilirubin elevation to > 1.5 X ULN (Table 57).

Table 57. Incidence of Treatment-emergent Peripheral Neuropathy in Eribulin-treated Subjects by Baseline Level of Liver Function Tests– Phase 2 / 3 Breast Cancer Trials

Category of Peripheral Neuropathy	All Eribulin-treated Subjects in Phase 2/3 Breast Cancer Trials (N=1503)					
	Normal LFT at Baseline (N=910) n (%)		ALT, AST or Bilirubin >1 x ULN at Baseline (N=589) n (%)		ALT, AST >3 x ULN or Bilirubin >1.5 x ULN at Baseline (N=83) n (%)	
	Grade of neuropathy during treatment:					
	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
Peripheral Neuropathy (narrow SMQ) [a]	266 (29.2)	60 (22.6)	179 (30.4)	44 (24.6)	31 (37.3)	9 (29.0)
Peripheral Neuropathy (broad SMQ) [b]	319 (35.1)	68 (21.3)	221 (37.5)	48 (21.7)	36 (43.4)	10 (27.8)

MedDRA version 14.1.
Percentages are based on the number of safety subjects in each integrated analysis set.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFT = liver function test; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standard MedDRA query; ULN = upper limit of normal.
a: Narrow SMQ analysis of peripheral neuropathy includes the following terms: allodynia, demyelinating polyneuropathy, hyperesthesia, neuropathy, neuropathy peripheral, painful response to normal stimuli, pallanesthesia, and paraesthesia.
b: Additional terms included in broad SMQ analysis: peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Source: SCS, Table 34.

Renal Impairment

Eribulin is minimally excreted via the kidney. Population PK analyses showed that renal impairment (CrCl) is not expected to significantly influence eribulin exposure. There were no patients with severe renal impairment included in the analysis. An ongoing study, E7389-A001-106, is being conducted to characterize the PK of eribulin in patients with moderate and severe renal dysfunction.

In the Phase 2/3 trials, renal failure was reported for four eribulin-treated subjects (0.3%) and renal failure acute was reported for three subjects (0.2%).

In general, eribulin-treated subjects with renal impairment had a similar safety profile compared with subjects with normal renal function.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions

No new data were submitted. However, given that eribulin showed inhibition of CYP3A4 *in vitro*, a PBPK modelling exercise has been performed to predict the effect on CYP3A4 substrates *in vivo*, which is discussed under Clinical Pharmacology above.

Drug-disease interactions

Subjects with diabetes are at risk for the development of peripheral neuropathy. Subgroup analysis of adverse reactions in eribulin-treated subjects with and without diabetes showed that diabetic subjects did not experience a significantly higher incidence of peripheral neuropathy per broad SMQ (39.8% vs. 34.9% in subjects with and without diabetes, respectively.

Post marketing experience

The post-marketing safety is handled in PSURs.

Gastro-intestinal perforation and disseminated intravascular coagulation have recently been added to the RMP as an Important potential risk and an Important identified risk, respectively.

Pancreatitis and disseminated intravascular coagulation have been added to the SmPC as a rare event on the basis of spontaneous reports received, for which a relationship to eribulin therapy could not be excluded.

2.5.2. Discussion on clinical safety

Safety populations and Exposure

The safety assessment is based on in total 1503 patients treated in phase 2-3 trials in metastatic/advanced breast cancer. This pooled safety population will be referred to as the Breast Cancer Population (BCP). Of the studies included in the BCP, studies 305, 201 and 211 were assessed at initial market approval; the neuropathy study 209 comparing eribulin and ixabepilone was assessed in FUM 015; the pooled data from studies 221 and 224 are assessed for the first time within the present application, together with the pivotal study 301 (number of eribulin-treated = 544).

The exposure was very similar in the eribulin and capecitabine arms of Study 301. This included e.g. mean and median duration of treatment (169 and 125 days, respectively, for eribulin compared with 173 and 119 days for capecitabine); and a relative dose intensity of 92% and 90%, respectively for eribulin and capecitabine.

Adverse events

The safety profile of eribulin is improved in the present disease setting, which includes 1st (21%) and 2nd line (51%) metastatic treatment, compared with the previously known safety profile based on later lines of therapy. Since Studies 305 and 301 were performed largely during the same time period, this difference in safety profile is not likely to be primarily an effect of improved management of patients following an increased experience of the drug, but appears to be chiefly explained by the earlier disease setting in Study 301.

Thus, three treatment-emergent adverse events (TEAEs) of special interest, i.e. asthenia/fatigue, peripheral neuropathy and arthralgia/myalgia; were clearly less frequent (7-17% lower) in this disease setting compared with the previously known safety profile (BCP), indicating that patients in earlier disease settings tolerate eribulin treatment better. However, the incidence of peripheral neuropathy is still high, around 21-27% and is considered an important safety problem, particularly since data from Study 209 (assessed in FUM 015) were not informative with regard to resolution of neuropathy.

In study 301, 8%/10% of patients had peripheral neuropathy by narrow/broad SMQ respectively, that had not resolved within 30 days of last dose. An additional 4% died or started new anti-cancer therapy within 30 days of last dose before neuropathy resolved. The worst case thus appears to be up to 12% or 14% (by narrow SMQ and broad SMQ, respectively) of eribulin-treated patients in this setting experiencing peripheral neuropathy not resolving within 30 days after last treatment. Peripheral neuropathy is an important identified risk in the RMP.

In this disease setting the safety profiles of eribulin and capecitabine, as described by frequencies of TEAE of any grade, are overall quite comparable (including asthenia /fatigue), with the exception of neutropenia/leukopenia, peripheral neuropathy, diarrhoea/vomiting, alopecia and palmar-plantar erythrodysaesthesia (PPE).

Severe (grade 3-4) adverse events

While overall lower frequencies of TEAEs of any grade were seen for eribulin-treated patients in Study 301 compared with previous studies, the frequencies of grade 3-4 (severe) TEAEs were more consistent compared with the previously known safety profile, although also in this regard lower frequencies were seen in some SOCs.

The differences between eribulin and capecitabine with regard to grade ≥ 3 TEAEs were in line with the known differences in their respective safety profiles, i.e. higher frequencies were seen for eribulin with regard to myelosuppression (46% vs. 5%, % for eribulin vs. capecitabine, respectively) and peripheral sensory neuropathy (3.3% vs. 0.5). In addition, hepatotoxicity grade ≥3 was more common with eribulin (1.1% vs. 0.4%), as was ALT increased (3.3 vs. 0.5%), while AST was similar (1.5 vs. 1.1%).

Capecitabine had higher frequencies of grade ≥3 diarrhoea (5.3 vs. 1.1%) and PPE (14.5% vs. 0%), as expected. It is noted that the incidence of grade ≥3 asthenia and fatigue were similar across arms, and that the difference in grade ≥3 febrile neutropenia was perhaps lower than expected (2.0% vs. 0.9% for eribulin vs. capecitabine, respectively), considering the very large differences in neutropenia.

Based on Broad SMQ, 116 patients (7.7%) in the Phase 2/3 breast cancer population experienced grade 3-4 peripheral neuropathy. 74 of these improved to grade 2 or lower, leaving 42 patients (2.8% of 1503) with remaining grade 3-4 neuropathy.

Serious adverse events and deaths

The Serious adverse event (SAE) profiles are consistent with the overall safety profiles of the two study drugs in Study 301, with approximately 3% more haematological SAEs in the eribulin group, but 3-2% more gastrointestinal, and nutrition-related (e.g. dehydration) SAEs in the capecitabine arm. It is noted that infections, cardiac disorders and asthenia/fatigue SAEs were similar across arms, numerically slightly more in the capecitabine arm. Two cases of toxic hepatitis SAEs were observed in the eribulin arm.

In Study 301, 26 of the 544 subjects (4.8%) in the eribulin group and 36 of the 546 subjects (6.6%) in the capecitabine group died during the treatment period or within 30 days of last dose of study treatment. In the eribulin arm, 9 deaths were associated with a TEAE (1.7 %), 2 had unknown cause of death, and 15 were attributed to disease progression. In the capecitabine arm, 13 deaths were associated with a TEAE (2.4%), 1 had unknown cause, and 22 were reported as due to disease progression.

Despite the differences in myelosuppressive potential, a TEAE with outcome of death (considered treatment-related) due to pancytopenia was observed in the capecitabine arm, and none in the eribulin arm; and the number of patients with fatal infections was the same in both arms.

Cardiac disorder TEAEs and Nervous system disorders TEAEs with outcome of death were more common in the capecitabine arm compared with the eribulin arm of Study 301.

Overall, there were no apparent qualitative differences in the TEAEs associated with death, apart perhaps from a case of toxic hepatitis in the eribulin arm.

AEs causing discontinuation

As seen for other entities of AEs, the frequencies of eribulin-treated patients discontinuing due to AEs generally as well as due to specific AEs are lower in study 301 compared with the previously known safety profile. Similarly, the small differences seen with regard to AEs causing discontinuation between the two treatment arms of Study 301 were in line with the safety profiles of eribulin and capecitabine, respectively. Four hepatobiliary events lead to discontinuation in the eribulin arm, 2 of which were noted as toxicity.

Laboratory abnormalities

- Myelosuppression

Shifts from CTC toxicity grade 0-1 at Baseline to grade 3-4 during treatment were most frequently recorded for Absolute neutrophil count (ANC). In the BCP, 60% of eribulin-treated subjects had a shift in ANC value from grade 0-1 at Baseline to Grade 3-4 sometime during treatment, compared to 58% of eribulin-treated subjects in Study 301 and 56% in Study 305. Overall, the frequencies of shifts in haematology laboratory tests in Study 301 were consistent with the previously known safety profile (or slightly improved). As before, haemoglobin and platelets rarely reached toxicity grade 3 or 4.

- Liver function tests

Out of 502 patients in the eribulin arm with baseline ALT grade 0 or 1, 104 (21%) had ALT shifts to grade 2 or 3 post baseline, and 37 (7%) had elevations to grade 3 (5-20 x ULN). A majority of these patients had their highest ALT elevation in cycles 1 and 2. Due to the presence of confounding factors (liver metastases, baseline elevated LFTs and/or cholestasis) in virtually all cases, no firm conclusions can be drawn on the relationship between eribulin and these grade 3 ALT elevations.

Liver toxicity grade ≥ 3was reported as a TEAE 1.1% of eribulin-treated patients in Study 301. While 3 patients fulfilled the laboratory criteria for Hy’ s, none of them fulfilled the clinical criteria of absence of other plausible explanation; in these cases in the form of progressing liver metastases or cholestasis.

The pattern of frequent early ALT increases considered of little or no clinical consequence and returning to normal in later cycles is acknowledged. This is sometimes referred to as “tolerance” and in the absence of bilirubin elevations is believed to have little or no potential for serious toxicity (The Clinical White Paper on DILI).

In the capecitabine arm, a shift to grade 2-4 ALT occurred in 10% of patients with baseline grade 0-1 (n= 500), i.e. clearly less frequently compared with the eribulin arm, while on the other hand treatment-emergent grade 2 bilirubin elevations were much more frequent (25% of patients with baseline grade 0-1).

Special populations

The safety of eribulin in the pivotal study was not affected by age in an apparent way in the BCP.

Japanese subjects enrolled in Study 221/224 had a very high rate of Grade 3-4 neutropenia (Grade 4 neutropenia occurred in 70.4% of subjects), not consistent with the results for any other trial in this submission. The addition of these subjects also affected the analysis of TEAEs by body surface area, otherwise without differences across groups. No biological basis for the high incidence of Grade 3-4 neutropenia in Study 221/224 was found. However, interim results of a post-marketing surveillance study in Japanese patients shows incidences of Grade 3-4 neutropenia and febrile neutropenia comparable to that observed in non-Japanese patients, potentially suggesting that the finding in Study 221/224 may not be representative of the clinical reality.

Hepatic impairment increase exposure to eribulin. There was an approximately 8% increase in peripheral neuropathy (by narrow and broad SMQ) for grade 1-2 events, and around 6% increase in grade 3-4 events, in patients with ALT or AST elevation to > 3 x ULN, or Bilirubin elevation to > 1.5 X ULN.

Diabetes is a risk factor for the development of peripheral neuropathy. However There was no increase of neuropathy in diabetic patients compared with non-diabetic patients.

2.5.3. Conclusions on clinical safety

In conclusion, the differences seen between eribulin and capecitabine with regard to TEAEs of toxicity grade ≥3 are consistent with the known differences in safety profiles and perhaps smaller than expected. It should be kept in mind that the labelled dose of capecitabine was used, which may be higher than optimal for some patients (NCCN).

At end of follow-up, 2.8% of the Phase 2/3 breast cancer population had remaining grade 3-4 neuropathy. Overall, this is not worse than for other tubulin-acting drugs. This was further assessed in Halaven MEA (FUM) 015.2, where the MAH presented data indicating that the peripheral neuropathy caused by eribulin may at least not be worse than that of other frequently used tubulin-acting chemotherapy agents with regard to overall frequency, grade ≥3 frequency, and add-on effects on pre-existing neuropathy. Furthermore, the MAH will investigate the frequency of resolution and time to resolution in the planned Phase 3 study E7389-A001-303 (ACCRU), including follow-up of neuropathy until death.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

No updated Risk Management Plan (RMP) has been submitted within this variation procedure.

The MAH states that “although this submission is for an indication which falls within the meaning of a ‘new indication’ in Module V, Guideline on Good Pharmacovigilance Practice, there is no significant change in the safety profile of Halaven and a revised Risk Management Plan is therefore not included.

The Summary of Ongoing Safety Concerns from the latest approved version of the RMP (V2.0) is shown below (

Table 58).

Table 58. Summary of Ongoing Safety Concerns (RMP V2.0)

Important identified risks	1. Myelosuppression and associated infections 2. Peripheral neuropathy 3. Nausea/Vomiting 4. Depression & Insomnia 5. Tachycardia 6. Disseminated intravascular coagulation
Important potential risks	1. Adverse Pregnancy Outcomes 2. Male infertility 3. Gastrointestinal perforation.
Important missing information	**Hepatic Impairment:** Eribulin has not been studied in patients with severe impaired hepatic function. **Renal impairment:** Based on the population pharmacokinetic analysis, renal impairment is not expected to significantly influence eribulin exposure. Eribulin is minimally excreted via the kidney. A renal impairment study has been initiated since the last RMP update at the request of the FDA: E7389-A001-106: An Open-label Phase I study to assess the Pharmacokinetics and Safety of HALAVEN in Subjects With Cancer Who Also Have Impaired Renal Function. It is anticipated that the study will be completed in March 2014. Any new findings will be reported and acted on as applicable. **Cardiovascular impairment:** Eribulin has not been studied in population with significant cardiovascular impairment and patients with history of congestive heart failure > NYHA Grade II, unstable angina or myocardial infarction within the past six months, or serious cardiac arrhythmia were excluded from the studies. **Elderly:** The safety of Eribulin (eribulin) in the elderly age group has not been established, although in breast cancer population (studies 201,211 and 305, N=827) 138 patients (16.7%) were ≥ 65 years of age and 17 patients (2.1%) were ≥ 75 years of age. In studies of 1222 patients treated with eribulin across multiple tumor types, 310 patients (25.4%) were ≥ 65 years of age, with 66 patients (5.4%) ≥ 75 years of age. The safety profile of eribulin in elderly patients (≥ 65 years of age) was similar to that of patients less than 65 years of age. No dose adjustments are recommended based on the age for elderly patients. Further studies ongoing in indication that will increase safety exposure under monitored circumstances. **Male patients:** Eribulin has not been studied in male patients with breast cancer but male patients have participated in Eribulin studies for prostate cancer and lung cancer. In clinical trials the adverse event profile of eribulin has been broadly consistent across various tumour types, including breast, prostate and lung cancer, so, while it is not anticipated that the risks from eribulin use in off-label oncology indications would differ significantly from those described previously, it is not possible to comment on tumour types which have not been

	studied in clinical trials. **Pediatric and Adolescent Population:** There has been no exposure in this population during clinical studies. **Pregnant women:** There has been no exposure in this population during clinical studies.

Source: EU RMP version 1.3 with version 2.0 as tracked changes (blue), from RMP procedure RMP018.

There are no new important risks identified in the present variation. No new pharmacovigilance activities in addition to those already being performed are considered needed to monitor the safety of the product. Thus, no update of the RMP is required at this point. It is expected, however, that future RMPs will be updated with relevant frequencies of ADRs as appropriate.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.5, 4.8, and 5.1of the SmPC have been updated. The Package Leaflet has been updated accordingly. Changes were also made to the PI to bring it in line with the current QRD template.

No user consultation has been submitted with this variation, which is considered acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Overall survival (OS) and progression-free survival (PFS) were both primary endpoints; none of them achieved statistically significant differences between study arms. Median OS was 15.9 vs. 14.5 months in the eribulin and capecitabine arms, respectively HR 0.879 (95% CI: 0.770, 1.003). The PFS analyses according to independent review (IRC) and investigator assessments (INV) generated very similar results. The HRs for PFS were 1.079 (95% CI: 0.932, 1.250) and 0.977 (95% CI: 0.857, 1.114), respectively. There were no statistically significant differences in objective response rates (ORR) between arms. The global QoL scores showed no meaningful changes during study, or differences between the eribulin and capecitabine arms. The QoL scores for the separate items were reflective of the two agents' respective ADR profiles.

The subgroup with 1 prior chemotherapy regimen for advanced disease (sought indication) had a HR consistent with the overall results, i.e. OS HR 0.84 (95% CI: 0.698, 1.010), and 49 days' (approximately 1.6 month) median difference in OS favouring eribulin. The PFS results of this subgroup were also consistent with the overall PFS results.

Uncertainty in the knowledge about the beneficial effects

The discrepancy between OS and PFS results are problematic since potentially suggesting that factors other than the study treatments could be affecting the OS results. The MAH has provided a large number of analyses investigating this issue. No factor has been identified that would imply over-estimation of the treatment effect associated with eribulin (see discussion on clinical efficacy).

Information on the efficacy of the combination of eribulin and HER2-targeted therapy is currently not included in the SmPC, since no such data have been submitted.

Risks

Unfavourable effects

The overall safety profile of eribulin was better in the present disease setting, which includes 1st (21%) and 2nd line (51%) metastatic treatment, compared with the previously known safety profile based on later lines of therapy. However, the incidence of peripheral neuropathy was still high, around 21-27%and is considered as an identified risk in the RMP.

Furthermore, in this disease setting the safety profiles of eribulin and capecitabine, as described by frequencies of TEAE of any grade, were overall quite comparable (including asthenia /fatigue), with the expected exceptions of neutropenia/leukopenia, peripheral neuropathy, and alopecia (more frequent for eribulin); and diarrhoea/vomiting and palmar-plantar erythrodysaesthesia (PPE) (more frequent for capecitabine).

Grade ≥ 3 ("severe") TEAEs frequencies were also mostly similar across study arms. Higher frequencies were seen for eribulin with regard to myelosuppression (46% vs. 5%, % for eribulin vs. capecitabine, respectively) and peripheral sensory neuropathy (3.3% vs. 0.5). In addition, hepatotoxicity grade ≥3 was more common with eribulin (1.1% vs. 0.4%). Capecitabine had higher frequencies of grade ≥3 diarrhoea (5.3 vs. 1.1%) and PPE (14.5% vs. 0%), as expected. It is noted that the incidence of grade ≥3 asthenia and fatigue were similar across arms, and that the difference in grade ≥3 febrile neutropenia was perhaps lower than expected (2.0% vs. 0.9% for eribulin vs. capecitabine, respectively), considering the very large differences in neutropenia. Thus, the differences seen between eribulin and capecitabine with regard to TEAEs of toxicity grade ≥3 are consistent with the known differences in safety profiles and perhaps smaller than expected.

Uncertainty in the knowledge about the unfavourable effects

There remains a clear lack of information concerning long-term persistence and resolution of eribulin-induced peripheral neuropathy. In Study 301, the worst case scenario appears to include up to 12% or 14% of eribulin-treated patients in this setting experiencing peripheral neuropathy (by narrow and broad SMQ, respectively) that did not resolve within 30 days after last treatment. Based on the phase 2/3 breast cancer population, 7.7% of patients experienced grade 3-4 peripheral neuropathy (by broad SMQ), and in 2.8% grade 3-4 neuropathy did not improve. The long-term resolution of peripheral neuropathy will be further addressed in a planned phase 3 study (E7389-A001-303, ACCRU) which has been included in the version of the RMP being assessed in the context of PSUV0018.

Information on the safety of the combination of eribulin and HER2-targeted therapy is currently not included in the SmPC, since no such data have been submitted.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Based on the presented data no statistically significant difference in efficacy has been shown for eribulin compared with capecitabine. Given the investigator-based PFS HR at 0.98 with a narrow 95% confidence interval (0.86, 1.11), a clinically relevant difference can be excluded.

The main ADRs affecting large proportions of eribulin-treated patients are neutropenia and neuropathy.

Neutropenia is not necessarily considered a major clinical problem, however, since routinely manageable with G-CSF. Peripheral neuropathy, on the other hand, if advanced is a debilitating condition affecting the daily life of patients. With earlier lines of therapy, the importance of persisting peripheral neuropathy after discontinuation of eribulin therapy naturally increases. Based on available data it appears that less than 3% have persisting grade 3-4 peripheral neuropathy, which is not considered unacceptable given the benefits.

Benefit-risk balance

Superiority was not demonstrated, and non-inferiority was not planned for. However, a clinically relevant difference in OS and PFS can be excluded.

There is a clear value in having two treatment options with different safety profiles, but similar tolerability. Taken together, the B/R for eribulin in the sought indication is positive.

Discussion on the Benefit-Risk Balance

A clinically relevant difference in terms of efficacy, however, between eribulin and capecitabine can be excluded based on a PFS HR 0.98 and narrow confidence intervals. Estimations, for the purpose of this discussion, based on the upper 95% confidence limits of the HR and the median PFS of the capecitabine arm suggests a small risk of eribulin having up to 2 weeks poorer PFS compared with capecitabine, based on investigator assessment. PFS differences of around 1-1.5 months are generally not considered to be of clinical relevance in the context of approval of oncology products; in line with this, the present uncertainty is accepted.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of Indication to include the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease.

As a consequence, sections 4.5, 4.8, 5.1 of the SmPC were updated. The Package Leaflet is updated in accordance.

The requested variation proposed amendments to the SmPC, and Package Leaflet.

This CHMP recommendation is subject to the following conditions:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.