Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Eribulin mesilate

Proprietary Product Name: Halaven

Sponsor: Eisai Australia Pty Limited

Date of First Round CER:
7 November 2011

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26 April 2012

TGA Health Safety Regulation

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Reports (CERs) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or details of post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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List of abbreviations

Table 1. List of abbreviations.

Abbreviation	Meaning
ADR	Adverse drug reaction
AE	Adverse event
Ae	Amount of unchanged drug excreted in urine
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration–time curve
BQL	Below quantitation limit
BSA	Body surface area
BUN	Blood urea nitrogen
CBR	Clinical benefit rate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL	Clearance
CL_R	Renal clearance
Cmax	Maximum observed concentration
CPK	Creatine phosphokinase
CR	Complete response
CRF	Case report form
CrCL	Creatinine clearance
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450

Abbreviation	Meaning
DLT	Dose limiting toxicity
DMC	Data monitoring committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen receptor
EU	European Union
FDA	Food and Drug Administration
Fe	Fraction of the dose excreted unchanged in the urine
FISH	Fluorescence in-situ hybridization
G	Grade
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony stimulating factor
HalB	Halichondrin B
Hb	Haemoglobin
HBs	Hepatitis B virus surface antigen
hCG	Human chorionic gonadotrophins
HCV	Hepatitis virus C
HER2/*neu*	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HR	Hazard ratio
i.v.	Intravenous
ICH	International Conference for Harmonization
ID	Identifier
IEC	Independent Ethics Committee

Abbreviation	Meaning
INR	International normalized ratio
IR	Incomplete response
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive voice recognition system
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LD	Longest diameter
LDH	Lactate dehydrogenase
MAD	Maximum acceptance dose
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRT	Mean residence time
MTD	Maximum tolerated dose
NCC	National Cancer Center
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-Free Survival
PgR	Progesterone receptor
PP	Per protocol
PR	Partial response
PT	Preferred term

Abbreviation	Meaning
PT	Prothrombin time
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
Sd	Standard Deviation
SOC	System organ class
SOP	Standard operating procedure
t1/2	Terminal phase half-life
TEAE	Treatment emergent adverse event
TEAV	Treatment-emergent abnormal laboratory values
Tmax	First time of occurrence of Cmax
TPC	Treatment of Physician's Choice
UK	United Kingdom
ULN	Upper limit of normal
UN	Unknown
USA	United States of America
γ-GTP	γ-glutamyl transpeptidase
λz	Terminal phase rate constant
Vz	Volume of distribution at the terminal phase

1. Introduction

Eribulin mesilate is a non-taxane, microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. Eribulin is a structurally simplified synthetic analog of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*. Eribulin is stated to inhibit the growth phase of microtubule dynamics without affecting the shortening phase, and to sequester tubulin into non-productive aggregates.

Therapeutic indication

The proposed indication for eribulin mesilate stated in the proposed Product Information (PI) is *"monotherapy for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments."*

> **Comment:** The proposed indication does not require that prior therapy should have included treatment with either capecitabine and/or vinorelbine. However, monotherapy with both capecitabine and vinorelbine could be used in Australia, consistently with their approved indications, for third-line treatment of locally advanced or metastatic breast cancer previously treated with taxanes and anthracyclines. If eribulin is approved for the proposed indication it will be an alternative to capecitabine and vinorelbine for treatment of the proposed patient population.

2. Clinical rationale

The sponsor's clinical rationale for developing eribulin is based on a "definite medical need for a new agent that prolongs life" in patients with advanced breast cancer that has recurred following initial therapy, and that is "reasonably well tolerated, and can be easily administered in an out-patient setting in order to improve patients' quality of life".

> **Comment:** The sponsor's rationale for developing eribulin is acceptable. Breast cancer is the most common cancer among women in Australian. [1] In Australia, capecitabine is the only drug specifically approved for the third-line treatment of locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. In addition, the approved broad indication of vinorelbine for the treatment of breast cancer in Australia could also support its use as monotherapy for the third-line treatment of locally advanced or metastatic breast cancer after anthracyclines and taxanes. However, there are no data suggesting that monotherapy with either capecitabine or vinorelbine provides an overall survival benefit for women with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. Consequently, there is a need for alternate treatments for women with this disease which can offer a survival benefit without causing undue toxicity.

In 2007, breast cancer accounted for 27.1% of all cancer diagnosed in women in Australia, and was the second most common cause of female deaths after lung cancer (2,680 and 2,911 deaths, respectively). It has been estimated that the mean age of first diagnosis of women with breast cancer in Australia is about 60 years, and the risk of breast cancer occurring in women to 75 years of age to be 1 in 11, increasing to 1 in 9 to 85 years of age.[1] The age standardised rates of death due to breast cancer in women in Australia fell from 30.8 deaths per 100,000 females in 1994 to 22.1 deaths per 100,000 females in 2007, and the five-year relative survival increased following a diagnosis of breast cancer from 72.6% between 1982-1986 to 88.3% between 2000-

[1] Australian Institute of Health and Welfare & Australian Association of Cancer Registries 2010. Cancer in Australia: an overview 2010. Cancer series no. 60. Cat. no. Can 46. Canberra. AIHW.

2006.[1, 2] In 2010, breast cancer was the leading cancer cause of burden of disease for females in Australia accounting for 61,000 disability-adjusted life years (DALYs) with 40,600 years of life being lost due to premature death and 20,500 years of healthy life lost due to disease, disability or injury.[1]

There are no national Australian data on the staging of breast cancer at the time of diagnosis or on relative survival rate according to breast cancer staging, but there are relevant state data from Queensland and NSW. In NSW (1995-2004), around 4% of breast cancer cases in all patients (women and men) were diagnosed when the breast cancer had spread to distant sites.[2] In NSW (1999-2003), the relative 5 year survival for all patients (women and men) diagnosed with breast cancer was lowest for those with "distant" breast cancer (41%) and highest for those with localised tumour (91%).[2] While the NSW data for diagnosis and relative survival based on staging relate to total breast cancer cases (i.e., women and men), it is likely that the data for women alone are virtually identical to the total data as nearly all the data relate to women with the disease (e.g. 99% of people with breast cancer between 1999 and 2003 in NSW were female).

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier documented a full clinical development program of pharmacology, efficacy and safety studies. The submission contained the following clinical information:

Module 5:

- 8 clinical pharmacology studies, including 8 that provided pharmacokinetic data and 4 that provided pharmacodynamic data.
- 1 population pharmacokinetic analyses.
- 2 Phase II dose finding studies.
- 1 pivotal Phase III study in patients with locally advanced and metastatic breast cancer previously treated with chemotherapy.
- 2 supportive Phase II efficacy and safety studies in patients with locally advanced and metastatic breast cancer previously treated with chemotherapy.
- 15 other completed or ongoing Phase I/II/III studies in patients with various advanced solid tumours submitted to support safety.
- 1 pooled analysis of efficacy and safety in all eribulin treated patients (AETP), 1 pooled analysis of efficacy and safety in eribulin treated breast cancer patients (BCP), 1 integrated summary of efficacy, 1 integrated summary of safety.
- References, sponsor's response to EMEA 120 questions.

Module 1:

Application letter, e-lodgement sheet, comprehensive Table of Contents (TOC), application forms, pre-submission details, patent certification, draft Australian PI and CMI, human embryo statement, draft Australian labels, information about the experts who prepared the sponsor's expert reports, GMP statement, information relating to pre-submission meetings between the sponsor and the TGA and meeting outcomes, statement relating to availability of individual

[2] Australian Institute of Health and Welfare & National Breast and Ovarian Cancer Centre 2009. Breast cancer in Australia: an overview, 2009. Cancer series no. 50. Cat. no. CAN 46. Canberra AIHW.

patient data, overseas regulatory status, FDA approved product label, European (UK) approved summary of product characteristics, statement relating to dataset similarities (US, Europe, Australia), statement from EMEA granting waiver from requirements to submit paediatric studies in patients with breast cancer, draft Risk Management Plan, environmental risk assessment for EMEA.

Module 2:

Quality Overall Summary, Nonclinical Overview, Clinical Overview, Nonclinical Summaries, Summary of Clinical Pharmacology Studies, Summary of Clinical Efficacy, Summary of Clinical Safety.

3.2. Paediatric data

The submission did not include paediatric data. It is considered that such data are not relevant to the submission.

3.3. Good clinical practice

Statements warranting that all Eisai sponsored studies had been conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) were provided in the clinical study reports (CSRs).

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

All key PK and PK/PD data from the 8, individual PK studies in patients with advanced solid tumours and the population-PK study are provided in the text of this evaluation report and their significance discussed. None of the PK studies had deficiencies that excluded their results from consideration. Table 2, below, shows the studies relating to each PK topic.

PK studies identified by the prefix E7389 are identified in this clinical evaluation report by their last three numbers (e.g. E7389-A001-101 is identified as study 101). E7389 was the code name for eribulin mesylate used throughout the submission, and in this clinical evaluation report the product will generally be referred to as eribulin.

Table2: Submitted clinical pharmacokinetic studies; n = subjects entered / evaluated.

Topic	Identification	Primary Aim	n
General PK – single dose	E7389-A001-101 E7389-A001-102 E7389-J081-105 NCI-5730	Dose escalation Dose escalation Dose escalation (Japan) Dose escalation	33 / 32 21 / 21 15 / 15 40 / 29
General PK – multi-dose	E7389-A001-101 E7389-J081-105	Dose escalation Dose escalation (Japan)	33 / 32 15 / 15
Mass balance	E7389-E044-103	Metabolism / Elimination	6 / 6
PK Special Populations	E7389-E044-108 Pop-PK Data Pop-PK Data Pop-PK Data Pop-PK Data None	Hepatic Impairment Renal Impairment Race Gender Age (Adults) Children/Adolescents	6 / 6

Topic	Identification	Primary Aim	n
PK Drug-Drug Interaction	E7389-E044-109	Eribulin and Ketoconazole	12 / 10
PK/PD and PD	E7389-E044-110	QTc interval	26 / 23
Population-PK – PKs, PK/AE, PK/PD	Pooled Phase I (101, 102, 103, 105, 108, 109, 110) and phase II data (211)		

In addition to the PK and PK/PD data derived from *in vivo* studies in humans with advanced solid tumours, the submission also included 8 *in vitro* studies using human biomaterials. These 7 studies are designated DSD2003-01, DS2004-03, DDDM2005-3, DMKP2003-13, DSD2001-31, DSDM2004-009, DDDA-2008-004 and DMPKM2010-003. Relevant information from these 8 studies have been included in the text of this clinical evaluation report.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated. In the pharmacokinetic analyses, eribulin concentrations and pharmacokinetic parameters were expressed as eribulin free base, and doses were expressed as the mesylate salt. Eribulin mesylate salt 1 mg is equivalent to 0.884 mg eribulin free base.

4.2.1. Pharmacokinetics in healthy subjects

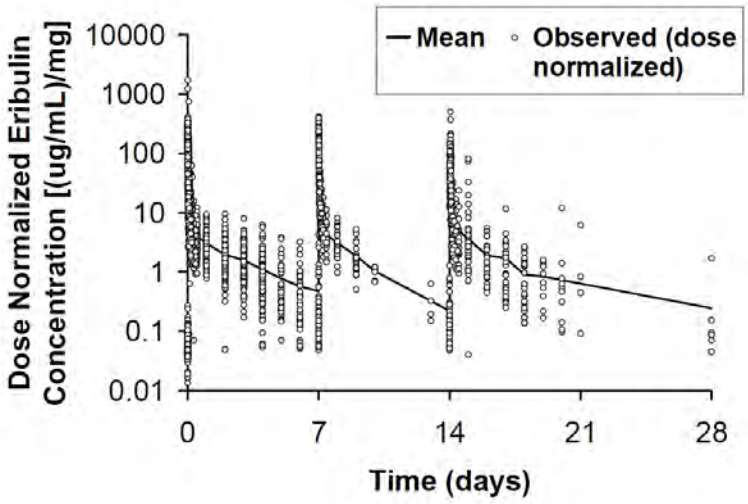
There were no PK studies in healthy subjects. This is standard procedure for cytotoxic agents.

4.2.2. Pharmacokinetics in the target population

All human *in vivo* PK and PK/PD data were derived from patients with advanced solid tumours from conventional individual PK studies and/or by the use of population PK methods. PK parameters were assessed using standard non-compartmental methods. The PK studies used validated liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS) to analyse plasma, urine, and faecal eribulin concentrations.

Following iv administration, variable PK results were observed across the range of studies for the same dose of eribulin. The population-PK study involved 2729 observations from 269 patients and demonstrated that the best final PK model for eribulin was a three compartment model with linear elimination. The PKs of eribulin are characterized by a rapid distribution phase followed by a prolonged elimination phase, with a long estimated mean terminal half-life of approximately 42 hours. The mean and individual observed dose-normalized plasma concentration versus time plot from the population-PK analysis is provided below in Figure 2. This plot includes data from 7 Phase I clinical pharmacology studies (101, 102, 103, 105, 108, 109, and 110), and 1 Phase II study (211).

Figure 2. Pop-PK Report – semi-log of mean observed dose normalised eribulin concentration data versus time.



The PK results for non-compartmental analysis from relevant studies in which eribulin was administered at a dose of 1.4 mg/m^2 are summarised below in Table 3.

Table3. Mean PK parameters from non-compartmental analysis.

Study ID; Day (D)	n	Dose * (mg/m^2)	CL L/hr/m^2	Vss L/ m^2	t½ hr	Cmax ng/mL	AUC$_{0-\infty}$ ng.hr/mL
101; D1	9	1.4	1.73 (CV 45%)	59.1 (CV 44%)	37.2 (CV 25%)	233 (CV 41%)	856 (CV 44%)
101; D15	4	1.4	1.88 (CV 52%)	47.3 (CV 17%)	35.6 (CV 52%)	247 (CV 41%)	913 (CV 76%)
105; D1	6	1.4	1.89 (CV 17%)	76.3 (CV 25%)	39.4 (CV 21%)	519 (CV 21%)	673 (CV 17%
105; D8	5	1.4	1.82 (CV 19%)	67.8 (CV 18%)	38.6 (CV 13%)	544 (CV 10%)	699 (CV 19%)
108; D1	6	1.4	2.33 (CV 31%)	84.6 (CV 42%)	36.1 (CV 24%)	186 (CV 36%)	600 (46%)
109; D1	9-10	1.4	1.55 (CV 56%)	77.0 (CV 39%)	45.6 (CV 30%)	207 (CV 36%)	971 (38%)

* Dose: 1.4 mg/m2 = 1.237 (free base equivalent). In study 101, 1.4 mg/m2 was administered as 1-hour iv infusion on Days 1, 8, and 15 of a 28-day cycle. In study 105, 1.4 mg/m2 was administered iv over 2 to 10 minutes on Days 1 and 8 of a 21-day cycle. In study 108, 1.4 mg/m2 was administered to patients with normal hepatic function (n=6) as iv bolus over 2-5 minutes on Days 1 and 8 of each 28-day cycle. In study 109, 1.4 mg/m2 was administered as an iv infusion over 2-5 minutes on Day 1.

4.2.2.1. Absorption

Eribulin mesylate 1.4 mg/m^2 is to be administered iv on Days 1 and 8 of a 21-day cycle, and no formulations other than intravenous are being proposed for registration.

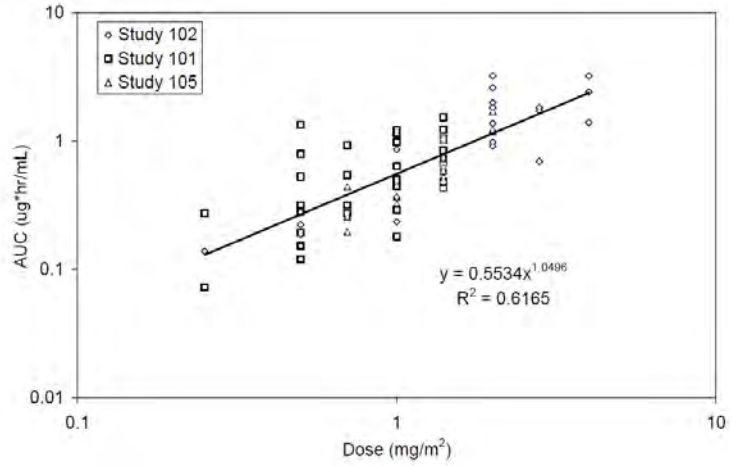
Sites and mechanisms of absorption: Not relevant.

Bioavailability: Not relevant. Intravenous formulations are by definition 100% bioavailable.

4.2.2.2. Dose proportionality

There was no formal dose proportionality study in the submission. However, the Module 2 data (Summary of Clinical Pharmacology Studies) explored the relationship between dose and AUC using combined exposure data from three Eisai dose-escalation studies in 68 evaluated patients [studies 101, 102, 105] (see Figure 3, below). The AUC of eribulin was dose-related over the dose range studied (0.25 to 4.0 mg/m^2). The relationship between dose and C_{max} was not explored as only one of the three studies used a bolus administration [study 105]. In the two other studies [101, 102], eribulin was administered as a 1 hour infusion, leading to schedule dependent differences in C_{max}. In the three studies, the CL, t½ and Vss were independent of dose, confirming the linear PKs of eribulin.

Figure 3: Relationship between dose and AUC pooled across the three Eisai dose-escalation studies.



4.2.2.3. Bioavailability during multiple-dosing

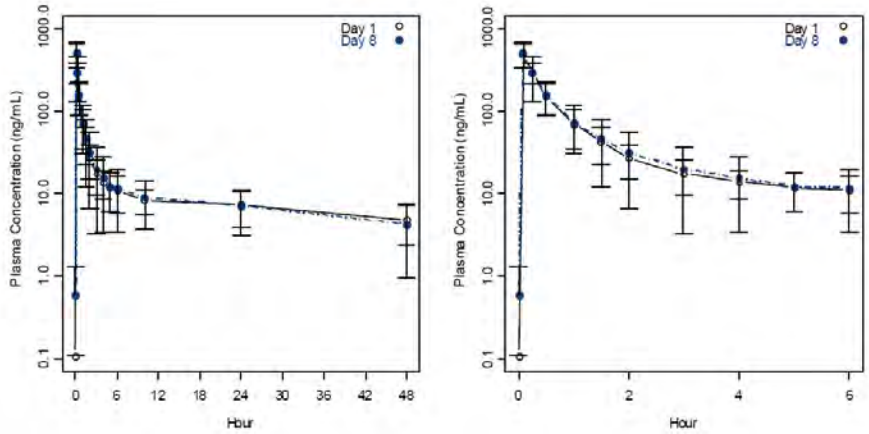
Information on the PK parameters of eribulin after single and multiple dose administration was included in the dossier. The PKs of eribulin following the 2nd or 3rd weekly dose in the first cycle were similar to the PKs following the 1st dose. Representative results from study 110 are provided below in Table 4 and Figure 4. In this study, eribulin 1.4 mg/m^2 was administered as an iv bolus dose over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. As samples for PK analysis were collected from 0 to 48 hours and the terminal elimination half-life of eribulin is ~42 hours, the $AUC_{0-\infty}$, t½,z, CL and Vss could not be estimated. Consequently, the study provided results for the AUC_{0-t} , C_{max}, t_{max}, T_{last}, and C_{last}.

Table4: Mean PK parameters following eribulin 1.4 mg/m^2 on Day 1 and Day 8; PK population (n=26).

Parameter	Cycle 1, Day 1 Mean (SD)	Cycle 1, Day 8 Mean (SD)
N	26	23
Actual data		
C_{max} (ng/mL)	516.5 (137.91)	502.4 (138.31)
t_{max} (hr)	0.08 (0.07 – 0.25)	0.08 (0.05 – 0.25)
$AUC_{(0\text{-}48\ hrs)}$ (ng.hr/mL)	628.1 (257.68)	629.1 (235.53)
Dose-normalized data		
C_{max} (ng/mL/mg)	239.6 (69.12)	234.3 (77.48)
$AUC_{(0\text{-}48\ hrs)}$ (ng.hr/mL/mg)	294.7 (133.54)	296.1 (138.86)

Data are shown as mean (SD), except for T_{max} which are median (range).

Figure4: Log-linear scale - mean (SD) plasma concentrations following eribulin 1.4 mg/m² on Day 1 and Day 8; PK population (n=26).



Comment: Overall, the data from all repeat doses studies and the representative data from study 110 showed that there was no accumulation of eribulin following repeat dosing. In study 110, the C_{max}, t_{max}, and AUC0-48 values were similar on Day 1 and Day 8 following eribulin 1.4 mg/m2 iv. Mean (SD) plasma concentrations immediately at the end of the infusion were 503.50 (134.67) ng/mL on Day 1 and 491.9 (149.60) ng/mL on Day 8. However, by 0.25 hours post infusion, mean (SD) plasma concentrations had fallen to 292.1 (128.13) ng/mL on Day 1 and 292.8 (80.27) ng/mL on Day 8. Mean (SD) plasma concentrations continued to fall rapidly and by 6 hours post-infusion, were 11.0 (6.27) ng/mL on Day 1 and 11.6 (6.14) ng/mL on Day 8. At 48 hours post-infusion, mean (SD) plasma concentrations were 4.8 (3.5) ng/mL on Day 1 and 4.3 (2.5) ng/mL on Day 8.

4.2.2.4. Effect of administration timing

No data.

4.2.2.5. Distribution

4.2.2.5.1. Volume of distribution

Eribulin has a large steady state volume of distribution (Vss) ranging from 41.0 to 114.2 L/m² in the single and multiple dose clinical pharmacology studies sponsored by Eisai.

4.2.2.5.2. Plasma protein binding

In vitro, mean (SD) plasma protein binding in humans (n=5) was 65.1% (3.79), 48.9% (13.24) and 50.0% (6.90) at eribulin concentrations of 100, 500 and 1000 ng/mL, respectively [DSD2001-38].

4.2.2.5.3. Erythrocyte distribution

In the mass balance study [103], mean blood/plasma ratio of total radioactivity ranged from 0.46 to 1.1, suggesting minimal preferential distribution of drug-derived radioactivity into red blood cells.

4.2.2.5.4. Tissue distribution

There are no data on tissue distribution in humans. However, the large volume of distribution suggests that the eribulin is extensively distributed to the tissues following iv administration.

4.2.2.6. Metabolism

4.2.2.6.1. Interconversion between enantiomers

Eribulin mesylate is a chiral compound containing 19 asymmetric centres. Consequently, the drug has the potential to undergo *in vivo* interconversion between enantiomers. The sponsor's

response to the EMEA's 120 day questions briefly summarises the results of an investigation into the drug's potential to undergo in vivo interconversion. Six randomly selected plasma samples, collected 90 minutes to 4 hours after eribulin administration from the ongoing, pivotal, Phase III study [301], were analyzed for eribulin and nine potential epimers. Concentrations of the majority of the epimers were below the limit of quantification. Three 3 epimers approached the quantifiable limit of the assays and represented 0.3% to 1.1% of eribulin. The sponsor concluded that the results demonstrated that eribulin undergoes minimal in vivo interconversion. The sponsor states that the observed minimal in vivo interconversion is unlikely to be of clinical relevance to the safety and efficacy profile of eribulin. The sponsor also stated that all of the potential isomers have been assessed for in vitro activity and found to be similarly active (albeit less so than eribulin). However, the sponsor provided no information on how in vitro activity was assessed.

4.2.2.6.2. Sites of metabolism and mechanisms / enzyme systems involved

In the mass balance study, total eribulin clearance was low (3.93 L/h). In the single-dose Eisai PK studies, total clearance ranged from 1.16 to 2.42 L/h/m^2. The major enzyme responsible the metabolism of eribulin *in vitro* (human liver microsomes) was CYP3A4, and the metabolites of eribulin formed by CYP3A4 reactions were mainly the isomeric monohydroxylates [DSD2003-01].

The *in vitro* metabolism of eribulin in humans was assessed using pooled human liver microsomes, pooled human liver cytosol, S9, or cDNA expressed recombinant Phase I or II metabolic enzymes. Pooled human liver microsomes metabolised eribulin (1 or 5 μM) by approximately 15% in a 30 minute incubation at 37°C, and CYP3A4 was believed to be the major enzyme responsible for eribulin metabolism. Recombinant CYP3A4 metabolised 1 μmol/L and 5 μmol/L eribulin by approximately 40% and 20%, respectively, in 30 minutes. Metabolism of eribulin by recombinant CYP3A4 was inhibited by CYP3A4-specific inhibitors. The metabolites formed by CYP3A4 mediated metabolism were mainly the isomeric monohydroxylates, but the sites of metabolic modification of the molecule could not be identified with current analytic methods. No metabolism of eribulin was clearly detected in the reaction mixtures containing pooled human liver cytosol, S9, or c-DNA phase I metabolic enzymes (CYP19, 1A1, 1A2, 1B1, 2A6, 2B6, 2C18, 2C19, 2C8, 2C9, 2E1, 3A5, 4A11, 4F2, 4F3A, 4F3B, FMO1, FMO3, and FMO5) or phase II metabolic enzymes (UGTA1, UGT1A3, UGT2B7, GSTA1-1, NAT1, NAT2, and SULT1A1), indicating a slow to moderate *in vitro* hepatic metabolic turnover. However, the investigators stated that CYP2D6, CYP2C9, CYP2C18, CYP3A5 and UDP-glycosyltranferases, such as UGT2B7, may possible play minor roles in eribulin metabolism.

4.2.2.6.3. Non-renal clearance

In the mass balance study, total eribulin total was 3.93 L/h and renal clearance was 0.301 L/h [103]. Therefore, it can be estimated that non-renal clearance is ~3.63 L/h (i.e., > 90% of total clearance). The relationship between total clearance and renal clearance observed in the mass balance study was consistently observed in all human PK studies in which both parameters were estimated (e.g. in study 102, the mean total CL was 1.76 L/h/m^2 and the mean renal CL was 0.203 L/h/m^2 in 21 patients across the dose range 0.25 to 4.0 mg/m^2).

4.2.2.6.4. Metabolites identified in humans

In vitro, the metabolites of eribulin formed by CYP3A4 reactions in human liver microsomes were mainly the isomeric monohydroxylates [DSD2003-01]. In the mass balance study [103], pooled plasma samples were profiled to determine relative concentrations of eribulin metabolites at the end of an infusion of ^{14}C-eribulin and then at 5, 15, 30 and 60 minutes post-dose. Unchanged eribulin accounted for over 90% of the radioactivity in all samples. No major metabolites were detected in the pooled samples and metabolite concentrations in each of the fractions were ≤ 0.6% of the eribulin concentration. Unchanged eribulin constituted almost the

entire drug-derived radioactivity in plasma, indicating that low concentrations of circulating metabolites are formed.

4.2.2.6.5. Active metabolites

No data in humans.

4.2.2.6.6. Other metabolites

No data in humans.

4.2.2.6.7. Pharmacokinetics of metabolites

No data in humans.

4.2.2.6.8. Consequences of genetic polymorphism

In the mass balance study [103], genotypes of CYP3A4, CYP3A5 and CYP2C9 were used to classify patients as extensive, intermediate or poor metabolisers. Dose normalized AUC and C_{max} were calculated for each patient and plotted by metaboliser status as determined by genotype. There was very little sequence variability in CYP3A4, CYP2C9, and CYP3A5 observed in this study population, with 5/6 patients being classified as CYP2C9 and CYP3A4 extensive metabolisers and 5/6 patients being classified as CYP3A5 poor metabolisers. Inspection of the dose normalised AUC and C_{max} plots for both eribulin and total radioactivity showed marked inter-subject variability in concentrations unrelated to CYP3A4, CYP2C9, or CYP3A5 genotype (i.e. metabolising classification).

In studies [108] and [109], genotypes of CYP3A4 and CYP3A5 were used to classify patients as extensive, intermediate or poor metabolisers, and AUC and C_{max} were summarised and plotted by metaboliser status as determined by genotype. However, in the population examined in study 108 there was no sequence variability in CYP3A4 (i.e., 17/17 patients classified as extensive metabolisers) and very little sequence variability in CYP3A5 (i.e., 16/17 patients classified as poor metabolisers). Similarly in study 109 all 10 patients were extensive metabolisers of CYP3A4 and poor metabolisers of CYP3A5.

> **Comment:** In the populations studies there were negligible or no genotypic variability in CYP3A4, CY3A5, and CYP2C9 metabolising enzymes. Consequently, no conclusions can be made on the potential relationship between metaboliser status based on CYP3A4, CY3A5, and CYP2C9 genotype and the marked variability observed in the PKs of eribulin.

4.2.2.7. Excretion

4.2.2.7.1. Routes and mechanisms of excretion

The mass balance study [103] showed that eribulin is excreted primarily unchanged in the faeces and to a lesser extent in the urine (see Table 5, below and discussion under Mass balance studies). In humans, metabolism represents a minor mechanism of excretion.

4.2.2.7.2. Mass balance studies

The metabolism and elimination of ^{14}C-eribulin was investigated in patients with advanced solid tumors in one mass-balance study [103]. Six patients (4 males; 2 females) of mean (SD) age 57.5 (13.4) years were given a 2 mg iv bolus dose of ^{14}C-eribulin acetate administered over 2 to 5 minutes on Day 1 of Cycle 1; actual dose ranged between 1.75 mg and 3.01 mg. Blood samples for PK determinations were collected prior to dosing, at the end of infusion, 5, 15, 30 minutes, and 1, 2, 4, 6, 8, and 10 hours after the end of infusion then on Days 2, 3, 4, 5, 6, 7 and 8 after dose during Cycle 1. The results are summarised below in Table 5.

Table5: Mean (SD) PK parameters for total radioactivity and eribulin in plasma: PK population.

Parameter	Total Radioactivity (N=6)	Eribulin (N=6)
C_{max} (ng eq/mL or ng/mL)	449 (136.6)	444 (144.0)
T_{max} (hr)	0.100 (0.07 – 0.20)	0.100 (0.07 – 0.20)
$t_{1/2}$ (hr)	42.3 (17.24)[a]	45.6 (8.68)
$AUC_{(0-t)}$ (ng eq.hr/mL or ng.hr/mL)	568 (391.6)	627 (385.8)
$AUC_{(0-inf)}$ (ng eq.hr/mL or ng.hr/mL)	753 (403.3)[a]	681 (425.4)
CL (L/hr)	-	3.93 (2.101)
CLr (L/hr)	-	0.301 (0.1257)
V_z (L)	-	247 (123.2)
Dose-Normalized parameter		
C_{max} (ng eq/mL/mg or ng/mL/mg)	224 (74.1)	222 (76.4)
$AUC_{(0-t)}$ (ng eq*hr/mL/mg or ng.hr/mL/mg)	269 (153.4)	301 (164.9)
$AUC_{(0-inf)}$ (ng eq*hr/mL/mg or ng.hr/mL/mg)	357 (148.2)	328 (189.1)

eq = equivalent; SD = standard deviation.
[a] n=5
Data are shown as mean (SD), except for T_{max} which are median (range).

Total recovery of the radioactive dose in urine and faeces for samples collected up to 312 hours post-dose was 90.4% (range 76.5 to 111%). Mean total recovery of eribulin in urine and faeces collected for up to 312 hr post-dose was 68.6% (range 48.4 to 87.4%). The results are summarised below in Table 6.

Table 6: Recovery of ^{14}C-eribulin related material and eribulin excreted in urine and faeces: PK population.

Parameter	Total radioactivity (N=6)	Eribulin (N=6)
Ae_{urine} (µg equiv or µg)	181 (79.8)	164 (75.5)
Ae_{feces} (µg equiv or µg)	1660 (409.4)	1268 (311.2)[a]
Ae_{total} (µg equiv or µg)	1841 (413.9)	1407 (352.4)[a]
Ae_{urine} (%)	8.92 (3.966)	8.10 (3.788)
Ae_{feces} (%)	81.5 (13.44)	61.9 (13.29)[a]
Ae_{total} (%)	90.4 (11.73)	68.6 (14.15)[a]

equiv = eribulin base equivalent; SD = standard deviation.
[a] n=5

Comment: This was a good quality mass balance study. Plasma exposure to eribulin (mean dose-normalized $AUC_{(0-t)}$ 301 ng.hr/mL/mg) was comparable to total radioactivity exposure (mean dose-normalized $AUC_{(0-t)}$ 269 ng eq.hr/mL/mg). The mean ratio eribulin concentration to total radioactivity in both blood and plasma was approximately unity at time-matched points for up to 72 hours after administration of ^{14}C-eribulin. These results suggest that the unchanged parent compound constitutes almost the entire drug-derived radioactivity in plasma, indicating that low concentrations of circulating metabolites are formed. The elimination half-life of eribulin (45.6 hours) was similar to the elimination half-life of the total radioactivity (42.3 hours). CLR (0.301 L/hr) represented a minor component (<10%) of total CL for eribulin (3.93 L/hr).

Eribulin derived radioactivity was excreted primarily in the faeces with total radioactivity accounting for 81.5% of the dose. Most of the total radioactivity (77.5%) was excreted in the faeces within 168 hours post-dose, and unchanged eribulin accounted for most of the total radioactivity (87.6%) excreted up to 72 hours post dose. The relative contribution of eribulin versus the total radioactivity slightly decreased at later time intervals (e.g. at 312 hours post dose, only 76.0% of the radioactivity recovered in faeces was parent drug). Recovery of the total radioactivity in the urine was 8.9% (range 5.42% to 16.4%), and unchanged eribulin represented most (~91%) of the total radioactivity excreted in the urine. Total radioactivity excretion in the urine was almost complete by 72 hour post dose.

4.2.2.7.3. Renal clearance

In the mass balance study [103], renal clearance was less than 10% of total clearance (see Table 6, above). This finding was confirmed across the range of PK studies in which it was assessed.

4.2.2.8. Intra- and inter-individual variability of pharmacokinetics

The population-PK study reported high inter-individual variance for the CL L/h (%CV = 45.6), with the CV% inter-occasion variance being 13.9%. Similarly, the inter-individual variance of the apparent volume of distribution was also high (CV% = 42.3). High intersubject PK variability can be anticipated at the proposed dose (see Table 3, above).

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

4.2.3.1.1. Study 108

The effects of hepatic impairment on the PKs of eribulin were examined in a Dutch, open, label, parallel-group, Phase I study in patients with advanced solid tumours and normal or mild and moderate hepatic impairment according to the Child-Pugh classification [study 108]. The study included 17 "White" patients (6 Normal, 7 Child-Pugh A [i.e. mild impairment], 4 Child-Pugh B [i.e. moderate impairment]), aged between 50 and 70 years (m/f = 11/8). Of the 7 patients with moderate hepatic impairment (Child-Pugh A), 1 had liver steatosis, 1 had chronic hepatitis, 1 had portal hypertension and oesophageal varices suggesting underlying liver disease, and 4 had extensive liver metastases. Of the 5 patients with mild hepatic impairment, all had liver metastases. There were no cases of hepatic cirrhosis in patients with mild or moderate hepatic impairment.

The PK parameters were assessed following the first dose of eribulin in Cycle 1. Eribulin was administered as an iv bolus over 2-5 minutes or diluted in up to 100 ml 0.9% sodium chloride for iv infusion over 2-5 minutes. The eribulin doses administered to patients with hepatic impairment were reduced relative to the 1.4 mg/m^2 dose for patients with normal function in order to prevent excessive toxicity expected to be caused by increased exposure to eribulin. Patients with moderate hepatic impairment received a lower eribulin dose (0.7 mg/m^2) than patients with mild hepatic impairment (1.1 mg/m^2).

The primary endpoints were the $AUC_{0-\infty}$ and C_{max}, and secondary endpoints included the AUC_{0-t}, tmax, t½, CL and Vss. Eribulin PK parameters were derived from plasma concentrations by non-compartmental analysis based on actual sample time, and the AUC and C_{max} were dose-normalized to account for differential doses across treatment groups. PK parameters for eribulin are summarised below in Table 7.

Table 7: Study 108 – Hepatic impairment; PK population.

Parameter	Normal (N = 6)	Child-Pugh A (N = 7)	Child-Pugh B (N = 4)
Dose administered: mg/m^2 IV	1.4	1.1	0.7
Dose-normalized to 1 mg			
$AUC_{(0-\infty)}$: ng.hr/mL/mg	229 (58.3)	420 (175.4)	721 (435.8)
C_{max}: ng/mL/mg	72.0 (20.22)	83.9 (28.54)	111 (44.0)
$AUC_{(0-t)}$: ng.hr/mL/mg	218 (53.3)	386 (161.5)	575 (328.6)
Actual values			
$AUC_{(0-\infty)}$: ng.hr/mL	600 (267.1)	731 (288.3)	795 (428.1)
C_{max}: ng/mL	186 (67.4)	147 (47.6)	126 (44.0)
$AUC_{(0-t)}$: ng.hr/mL	571 (243.1)	671 (258.6)	638 (320.4)
t_{max}: hr	0.330 (0.03-0.37)	0.350 (0.33-0.47)	0.325 (0.25-0.35)
$t_{1/2}$: hr	36.1 (8.65)	41.1 (12.73)	65.4 (21.33)
CL: L/hr	4.57 (0.959)	2.75 (1.094)	1.86 (1.065)
V_{ss} : L	166 (50.1)	113 (29.1)	130 (79.8)
CL and V_{ss} normalized to BSA			
CL: L/hr/m^2	2.33 (0.729)	1.55 (0.626)	0.96 (0.474)
V_{ss}: L/m^2	84.6 (35.64)	63.4 (16.23)	69.7 (42.97)

Data are shown as mean (SD), except for t_{max} which is median (range)

The study included an assessment of the relative bioavailability (exposure data normalized to a dose of 1 mg) of eribulin in patients with hepatic impairment and patients with normal function (see Table 8, below). These results showed that increasing exposure to eribulin was directly related to increasing renal impairment.

Table 8: Relative bioavailability of eribulin: PK population.

Parameter	Geometric Least Square Means		Comparison	Ratio [a]	90% Confidence Interval
	Impaired	Normal			
$AUC_{(0-\infty)}$ ng.hr/mL/mg	390	223	Child-Pugh A: Impaired vs. Normal	1.75	(1.16 - 2.65)
	622		Child-Pugh B: Impaired vs. Normal	2.79	(1.72 - 4.51)
$AUC_{(0-t)}$ ng.hr/mL/mg	361	213	Child-Pugh A: Impaired vs. Normal	1.70	(1.15 – 2.50)
	507		Child-Pugh B: Impaired vs. Normal	2.38	(1.52 – 3.73)
C_{max} ng/mL/mg	80.3	69.9	Child-Pugh A: Impaired vs. Normal	1.15	(0.827 - 1.59)
	104		Child-Pugh B: Impaired vs. Normal	1.48	(1.01 - 2.17)

a: Ratio of treatment means was Impaired: Normal

4.2.3.1.2. Population-PK Report

The population-PK report included an analysis of the exposure data from the hepatic impairment PK study [study 108]. The report noted that clearance in patients with moderate hepatic impairment eribulin clearance was more than 2-fold lower relative to patients with normal hepatic function. However, a box and whisker plot included in the report showed that the ranges of expected AUC for patients with normal and moderate hepatic function administered 1.4 mg/m^2 and 0.7 mg/m^2, respectively, resulted in similar exposures in both patient groups. In addition, 95% prediction interval of concentration versus time plots included in the report showed similar predicted exposures in patients with normal hepatic function treated with 1.4 mg/m^2 and patients with moderate hepatic impairment (Child-Pugh B) treated with 0.7 mg/m^2.

The population-PK analysis also found that the probability of patients experiencing Grade 4 neutropenia (based on reported AEs) is related to eribulin AUC and aspartate transaminase

(AST) levels. Patients with high AST levels (potentially indicating poor hepatic function) appear to be more likely to experience Grade 4 neutropenia than patients with normal AST levels. Exposure to higher eribulin concentrations (AUC) resulted in a proportionally greater probability of Grade 4 neutropaenia in patients with normal and elevated AST levels. The probability of experiencing a Grade 4 neutropaenia ranged from 4% (AUC 500 µg.hr/L) to 13% (AUC 2500 µg.hr/L) in patients with normal AST levels (40 IU/L), with the percentages for the corresponding AUCs being 7% and 25% for patients with elevated AST levels of 100 IU/L, and 13% and 35% for patients with elevated AST levels of 200 IU/L.

In patients with moderate hepatic impairment, treatment with the lower recommended dose of 0.7 mg/m^2 decreased the probability of experiencing Grade 4 neutropenia compared with treatment with the normal dose of 1.4 mg/m^2. However, due to elevated AST levels in patients with moderate hepatic impairment, the probability of experiencing Grade 4 neutopenia with the 0.7 mg/m^2 dose would still be higher than the probability of a patient with normal hepatic function experiencing Grade 4 neutropaenia with the 1.4 mg/m^2 dose. In patients with moderate hepatic impairment receiving the 0.7 mg/m^2 dose, the expected average probability of experiencing Grade 4 neutropenia was predicted to be ~15%.

The population-PK analysis also showed that albumin, bilirubin and alkaline phosphatase levels were predictors of eribulin clearance. Over an albumin range from 1.50 g/dL to 4.50 g/dL, clearance ranged from 0.91 to 2.0 L/h; over a bilirubin range from 0.10 to 5.0 g/dL, clearance ranged from 4.56 to 2.06 L/h; and over an alkaline phosphatase range from 27 to 1265 IU/L, clearance ranged from 2.99 to 1.73 L/h.

4.2.3.1.3. Sponsor's response to EMEA's 120 day questions

Further information on the use of eribulin in patients with hepatic impairment were presented in the sponsor's response to the EMEA's 120 day questions. The EMEA suggested that recommendations in the SmPC on starting dose in hepatic impairments should "if possible" be based on serum liver function tests (bilirubin/AST/ALP) "since these are routinely assessed in cancer patients and related to the presence of and degree of liver metastases". The sponsor responded that the dosing recommendations were based on the results of the definitive Phase I study in patients with hepatic impairment (i.e., study 108). The sponsor provided eribulin exposure versus time data comparing the predicted profiles (median concentration and 90% CIs) of patients with normal hepatic function to patients with elevated ALP levels in the range 220 to 800 IU/L, patients with bilirubin levels within the range 0.75 to 4 mg/dL, and patients with albumin levels in the range 2 to 4 g/dL. Examination of the eribulin exposure versus time plots for the three scenarios indicates that no reliable dosing recommendations can be made based only on ALP, bilirubin or albumin levels.

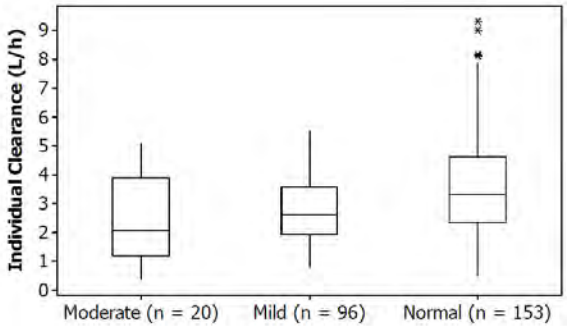
> **Comment:** Study 108 was a good quality study in patients with hepatic impairment. It showed that increasing hepatic impairment resulted in increasing exposure to eribulin. In patients with mild and moderate hepatic impairment mean dose normalized $AUC_{0-\infty}$ was about 1.8 and 2.8-fold higher, respectively, relative to patients with normal hepatic function. The mean dose normalized C_{max} also increased in patients with hepatic impairment relative to patients with normal hepatic function (about 1.2 and 1.5-fold higher for mild and moderate impairment, respectively). The 90% CIs for the dose normalized AUC and C_{max} ratios (impaired:normal) were all outside the accepted bioequivalence limits of 0.8 to 1.25. Hepatic impairment also decreased clearance and prolonged the elimination half-life of eribulin, with changes being more marked in patients with moderate impairment than in patients with mild impairment.
>
> The population-PK analysis predicts similar exposure to eribulin in patients with moderate hepatic impairment treated with eribulin 0.7 mg/m2 and patients with normal hepatic function treated with 1.4 mg/m2. However, the analysis also predicts that the probability of experiencing Grade 4 neutropenia is greater in patients with moderate

hepatic impairment treated with eribulin 0.7 mg/m^2 than in patients with normal function treated with 1.4 mg/m^2. This increased risk, despite similar eribulin exposures, appears to be related to increased ALT levels in patients with hepatic impairment compared with patients with normal hepatic function. The population-PK analysis noted that unexplained variability in both the PK and adverse event models was high. Overall, the sponsor maintained that the population-PK models were "adequate to confirm a dose adjustment to 0.7 mg/m^2 for patients with moderately impaired hepatic function." The proposes PI recommends that patients with mild hepatic impairment (Child-Pugh A) be treated with 1.1 mg/m^2 and patients with moderate hepatic impairment (Child-Pugh B) be treated with 0.7 mg/m^2. It is considered that the proposed recommendations are consistent with the available data.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

There were no specific studies in patients with impaired renal function. However, the mass balance study [103] showed that renal clearance (0.301 L/h) was < 10% of total clearance (3.93 L/h), and . unchanged eribulin excreted in the urine accounted for ~ 8.1% of the total dose. The three Eisai dose escalation studies also showed minimal renal elimination of eribulin with < 10% of the dose being recovered in the urine. The population-PK analysis showed that median eribulin clearance was lower in patients with mild renal impairment (80 mL/min < CrCL ≥ 50 mL/min) and moderate renal impairment (50 mL/min < CrCL ≥ 30 mL/min) compared with patients with normal renal function (CrCL > 80 mL/min) (see Figure 5, below). There were no data on renal clearance patients with severe renal impairment in the population-PK analysis.

Figure 5: Effect of Renal Function (mild and moderate impairment) on eribulin clearance.



Note: the bottom and top edges of the box correspond to the sample 25th (Q1) and 75th (Q3) percentiles. The box length is one interquartile range (Q3 - Q1). The centre horizontal line corresponds to the sample median. The vertical lines (whiskers) represent the data range up to 1.5 interquartile. The asterisks (*) denote outliers.

4.2.3.2.1. Sponsor's response to EMEA's 120 day questions

The sponsor provided additional information on patients with renal impairment in its response to the EMEA's 120 day questions. Based on these data, the sponsor concluded that no dose adjustments are recommended for patients with renal impairment. The sponsor referred to the results from a Phase I/II study sponsored by the NCI (reported in abstract form) in patients with advanced urothelial cancers which showed a non-statistically significant trend towards increasing eribulin exposure (assessed by the AUC) and decreasing total clearance with worsening renal function (see Table 9, below). This Phase I/II study (Synold *et al*., 2010) included a Phase I component in subjects with moderate renal impairment (CrCL ≥ 49 to 59 mL/min) and severe renal impairment (CrCL 0-40 mL/min not responding to dialysis) treated with eribulin 1.4 mg/m^2 given as an iv bolus over 1-2 minutes. The study abstract reported no DLTs at the MTD of 1.4 mg/m^2 in patients with moderate renal impairment. However, in

patients with severe renal impairment DLT was experienced by 1 patient at 1.4 mg/m^2 (Grade 3 muscle weakness and hypoalbuminaemia). No further DLTs were observed at 1.4 mg/m^2 in an expanded cohort of 6 patients, leading the authors to conclude that the MTD in patients with severe renal impairment was 1.4 mg/m^2.

Table 9: Synold *et al*, 2010 – PKs of eribulin in patients with normal and impaired renal function.

Cohort	N	Dose level mg/m^2	Mean (standard deviation)			
			Day 1 CrCl mL/min	$AUC_{0\text{-}72h}$ nM.h	$AUC_{0\text{-}inf}$ nM.h	CL L/h
Normal	5	1.4	103 (50)	1626 (715)	2375 (1031)	1.9 (0.7)
Moderate	6	1.4	45 (4)	1897 (946)	2617 (1745)	1.8 (0.8)
Severe	4	1.4	25 (2)	2848 (1472)	3876 (2908)	1.4 (1.3)

AUC = area under the concentration-time curve, CL = clearance, CrCl = creatinine clearance.
Data source: Synold et al, 2010.

Source: Sponsor's response to EMEA day 120 questions.

The sponsor also provided a PK analysis in patients with renal impairment based on pooled dose normalized $AUC_{0\text{-}\infty}$ data collected from 6 Phase 1 studies (101, 102, 103, 105, 108, and 109). The results showed that the mean $AUC_{0\text{-}\infty}$ was higher in patients with renal impairment compared with patients with normal renal function, and was higher in patients with moderate renal impairment than in patients with mild renal impairment (see Table 10, below).

Table 10: Descriptive statistics of pooled dose-normalized $AUC_{0\text{-}\infty}$ by renal function.

Parameter	Normal Renal Impairment (CrCl>80 mL/min)	Mild Renal Impairment (30>CrCl≥80 mL/min)	Moderate Renal Impairment (CrCl<30 mL/min)
n	62	34	5
Mean (SD)	0.62 (0.277)	0.81 (0.446)	1.05 (0.655)
Geomean	0.561	0.71	0.856
Median	0.58	0.69	1.2
Min, Max	0.2, 1.48	0.27, 2.15	0.34, 1.83

$AUC_{(0\text{-}inf)}$ = area under the concentration × time curve from time zero to infinity, $AUC_{(0\text{-}inf)}D$ = Dose normalized exposure, CrCl = creatinine clearance, SD = standard deviation.

Source: Sponsor's response to EMEA day 120 questions.

In addition, the sponsor provided a separate analysis of eribulin dose normalized exposure data based on the $AUC_{0\text{-}48\,h}$ in patients with renal impairment from study 110 (see Table 11, below). The results showed that the mean $AUC_{0\text{-}48h}$ was higher in patients with renal impairment compared with patients with normal renal function, and was higher in patients with mild renal impairment than in patients with moderate renal impairment.

Table 11: Descriptive statistics of dose-normalized $AUC_{0\text{-}48\,h}$ by renal function.

Parameter	Normal Renal Impairment (CrCl>80 mL/min)	Mild Renal Impairment (30>CrCl≥80 mL/min)	Moderate Renal Impairment (CrCl<30 mL/min)
n	12	11	3
Mean (SD)	0.23 (0.074)	0.35 (0.132)	0.34 (0.255)
Geomean	0.223	0.326	0.285
Median	0.22	0.3	0.25
Min, Max	0.13, 0.37	0.19, 0.56	0.15, 0.63

$AUC_{(0\text{-}48h)}$ = area under the concentration × time curve from time zero to 48 hours, CrCl = creatinine clearance, SD = standard deviation.

Source: Sponsor's response to EMEA day 120 questions.

Comment: The submission included no formal PK studies in patients with renal impairment. The population-PK analysis showed that eribulin was lower in patients with mild and moderate renal impairment compared with patients with normal renal function. Furthermore, eribulin clearance was lower in patients with moderate renal impairment compared with mild renal impairment. The results suggest a trend towards decreased eribulin clearance with increased renal impairment. In Synold *et al*, 2010, a similar but

not statistically significant trend towards increasing exposure (AUC) and decreasing clearance with worsening renal function was noted.

The PI recommends that patients with severely impaired renal function (CrCL < 40 mL/min) may need a dose reduction and states that the optimal dose for this patient group has not been established. No specific dose adjustments are recommended for patients with mild to moderate renal impairment. The PI also stated that a study in patients with different degrees of impaired renal function showed that the exposure of eribulin in patients with moderate renal function (CrCL ≥ 40 to 59 mL/min, n=6) was similar to patients with normal renal function while the exposure in patients with severe impairment was increased by 75% (CrCL < 40 mL/min, n=4). The study referred to in the PI is the Synold *et al*, 2010 abstract and the exposure data referred to in the PI are based on the $AUC_{0\text{-}72h}$ results from this study.

The recommendations in the PI relating to dosing in patients with renal impairment are identical to those in the UK SPC. In contrast, the US label recommends that the dose in patients with moderate renal impairment (CrCL 30-50 mL/min) should be reduced to 1.1 mg/m^2. In addition, the US label states that available data suggests that no dose adjustment is necessary for patients with mild renal impairment (CrCL 50-80 mL/min). The US label states that for patients with moderate renal impairment (CrCL 30-50 mL/min), the geometric mean dose-normalized systemic exposure increased 2-fold compared to patients with normal renal function. Furthermore, in a public document the sponsor states "the geometric mean dose-normalized systemic exposure increased two-fold compared to patients with normal renal function". In a publically available document apparently released after the current submission was compiled, the sponsor recommends a lower starting dose of 1.1 mg/m^2 for patients with moderate renal impairment [Eisai FDA Advisory Subcommittee Briefing Document; October 25, 2010]. This statement contrasts with that in the current submission which states that, based on the results of the NCI study and the submitted population-PK analysis, renal impairment is not expected to have "a substantial effect on eribulin exposure".

Overall, the data from the 6 Phase I studies and Synold *et al*, 2010 showed that there was a relationship between increasing exposure to eribulin and deteriorating renal function. The sponsor has stated in a public document that mean dose-normalized systemic exposure increased 2-fold in patients with moderate renal impairment and that the eribulin mesylate dose should be reduced to 1.1 mg/m^2 in patients with moderate renal impairment. Based on the available, but unconfirmed data, it is recommended that the dose should be adjusted in patients with renal impairment in line with the sponsor's public statement.

4.2.3.3. Pharmacokinetics according to age

There were no formal studies examining the effect of age on the PKs of eribulin. However, the population-PK analysis compared the effect of age on eribulin clearance (i.e., patients aged < 65 years [n=206] vs patients aged ≥ 65 years [n=63]). Inspection of the box and whisker plots for clearance showed no notable difference between patients aged < 65 years and patients aged ≥ 65 years. The mean (SD) age (n=269) in the population-PK study was ~57 (11) years with a range of 27 to 81 years.

4.2.3.4. Pharmacokinetics according to gender

There were no formal studies examining the effect of gender on the PKs of eribulin. However, the population-PK analysis compared the effect of gender on eribulin clearance (i.e., male [n=55] vs female [n=214]). Inspection of the box and whisker plots for clearance showed no notable difference between males and females.

4.2.3.5. Pharmacokinetics related to race

There were no formal studies examining the effect of race on the PKs of eribulin. However, the population-PK analysis examined the effect of race on eribulin clearance, and inspection of the box and whisker plots showed no notable difference among the examined racial groups. However, these results should be interpreted cautiously as the majority of patients in the analysis were white (n=184, 68.5%), with the remaining groups being black (n=14, 5.2%), Asian non Japanese (n=4, 1.5%), Japanese (n=12, 4.5%), hispanic (n=10, 3.7%), and other (n=4, 1.5%). The population-PK analysis also included a comparison of the mean dose normalized eribulin plasma concentration versus time curves for Caucasian and Japanese subjects, and inspection showed the curves to be virtually superimposable.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

4.2.4.1.1. Study 109 – Eribulin versus Ketoconazole (CYP3A4 inhibitor)

The submission included one Phase I, randomised, open-label, 2-treatment, 2-sequence, 2-way crossover study in patients with advanced solid tumors that compared the PKs of eribulin following eribulin with and without ketoconazole (a potent CYP3A4 inhibitor). In Cycle 1, patients were randomly allocated to one of two treatment sequences (Group 1 or Group 2): patients in Group 1 received eribulin 1.4 mg/m^2 on Day 1 followed by eribulin 0.7 mg/m^2 plus ketoconazole 200 mg on Day 15 and ketoconazole 200 mg alone on Day 16; and patients in Group 2 received eribulin mesylate 0.7 mg/m^2 plus ketoconazole 200 mg on Day 1, ketoconazole 200 mg alone on Day 2 followed by eribulin 1.4 mg/m^2 on Day 15. The study enrolled 6 patients in both Groups 1 and 2, and 4 and 6 patients in Groups 1 and 2 , respectively, completed the PK study phase.

PK blood sampling was performed pre-dose, and post-dose for up to 144 hours following administration of eribulin (with and without ketoconazole) on Days 1 and 15 during the first cycle of treatment only (study phase). After PK assessments in the first cycle, patients could continue to receive eribulin at a dose of 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle (extension phase). The PK results are summarised in Table 12.

Table 12: Eribulin PKs following administration of eribulin with and without ketoconazole: PK population.

Parameter	n	Eribulin	n	Eribulin + Ketoconazole
Dose administered: mg/m^2 IV		1.4		0.7
Dose-normalized				
$AUC_{(0\text{-}t)}$ (ng.hr/mL/mg)	10	313 (116.6)	10	326 (133.2)
$AUC_{(0\text{-}\infty)}$: (ng.hr/mL/mg)	9	406 (159.3)	7	410 (204.9)
C_{max}: ng/mL/mg	10	86.4 (33.33)	10	89.2 (31.89)
Actual values				
$AUC_{(0\text{-}t)}$ (ng.hr/mL)	10	846 (301.2)	10	441 (177.9)
$AUC_{(0\text{-}\infty)}$: (ng.hr/mL)	9	971 (371.9)	7	482 (241.5)
C_{max} (ng/mL)	10	207 (73.9)	10	106 (33.7)
t_{max}: hr	10	0.360	10	0.365
$t_{(1/2)}$: hr	9	45.6 (13.62)	7	40.5 (7.69)
CL: L/hr	9	3.10 (1.903)	7	3.37 (2.507)
CL: L/hr/m^2	9	1.55 (0.866)	7	1.67 (1.051)
V_{ss} : L	9	153 (63.4)	7	141 (83.7)
V_{ss}: L/m^2	9	77.0 (29.66)	7	70.2 (34.75)

Data are shown as mean (SD), except for t_{max} which are median values

Eribulin administered with and without ketoconazole were bioequivalent as regards eribulin exposure assessed by both the dose normalized $AUC_{0\text{-}\infty}$ and the C_{max} (Table 13, below).

Table 13: Statistical analysis of primary PK parameters: PK evaluable population.

Parameter	Geometric Least Square Means		Ratio of treatment means (Eribulin plus ketoconazole: eribulin)	90% Confidence Interval
	Eribulin plus ketoconazole	Eribulin		
$AUC_{(0-\infty)}$ (ng.hr/mL/mg)	379	400	0.950	(0.804, 1.121)
C_{max} (ng/mL/mg)	81.0	83.9	0.966	(0.834, 1.118)

Note: $AUC_{(0-\infty)}$ and C_{max} are normalized to 1 mg of free form eribulin. Model includes terms for treatment, period (day) and patient. Patient is included as a random effect.

Comment: This was a good quality PK interaction study. Patients were administered eribulin 1.4 mg/m^2 alone and a reduced dose of 0.7 mg/m^2 when co-administered with ketoconazole (in anticipation of significant inhibitory effects on CYP3A4 mediated eribulin metabolism). The study showed that co-administration of ketoconazole and eribulin had no significant effect on eribulin exposure. This suggests that, although eribulin is primarily metabolised by CYP3A4, inhibition of this enzyme has no significant effects on eribulin exposure.

4.2.4.2. Clinical implications of in vitro findings

- In study DMPK2000-13, eribulin did not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 at concentrations up to 5 µM (i.e. up to 3650 ng/mL eribulin free base). However, eribulin at a concentration of 5 µM (i.e. up to 3650 ng/mL eribulin free base) statistically significantly inhibited CYP3A4 compared with control ($p<0.05$). The highest mean C_{max} observed in the Phase I clinical pharmacology studies was 718 ng/mL following administration of a single 2 mg/m^2 dose of eribulin mesylate [105]. Therefore, the observed *in vitro* inhibition of CYP3A4 by eribulin at a concentration of 3650 ng/mL (free base) is unlikely to be clinically relevant. Overall, it can be concluded that there is little likelihood that eribulin at clinically expected plasma concentrations will result in significantly increase exposure to co-administered drugs that are metabolized by CYP1A2, CYP2C9, CYP2C19, CYP2D6 CYP2E1, or CYP3A4.
- In study DSD2004-03, eribulin did not induce CYP1A or CYP3A at concentrations of 0.05 to 5 µM (i.e., up to 3650 ng/mL eribulin free base). Consequently, it can be concluded that there is little likelihood that eribulin at clinically expected plasma concentrations will reduce exposure to co-administered drugs that are metabolized by CYP1A or CYP3A4.
- In study DDDM2005-003/DDD2005-46, eribulin did not induce CYP2C9 or CYP2C19 at concentrations of 1 to 10 µM (i.e. up to 7300 ng/mL eribulin free base). Consequently, it can be concluded that there is little likelihood that eribulin at clinically expected plasma concentrations will reduce exposure to co-administered drugs that are metabolized by CYP2C9 or CYP2C19.
- In study DSD2001-31, eribulin inhibited CYP3A4 at apparent Ki values of 3 to 17 µM (i.e. 2190 to 12410 ng/mL of eribulin free base). Inhibition was reversible and competitive. The highest mean C_{max} observed in the Phase I clinical pharmacology studies was 770 ng/mL. Therefore, the observed *in vitro* inhibition of CYP3A4 by eribulin at concentrations of 2190 to 12410 ng/mL (eribulin free base) is unlikely to be clinically relevant.
- In study DSDM2004-009, eribulin suppressed the activities of CYP3A4-mediated testosterone 6β-hydroxylation and midazolam 1'-hydroxylation with apparent Ki values of 25-30 µM and 10-15 µM, respectively (i.e. 7300 to 21900 ng/mL eribulin free base). Ketoconazole (5 µM), a potent CTP3A4 inhibitor, suppressed the metabolism of eribulin (1-10 µM [730-7300 ng/mL eribulin free base]). In contrast to the potent inhibition shown by ketoconazole, eribulin at concentrations up to 10 µM (i.e. up to 7300 ng/mL free base) elicited minimal inhibitory effects on CYP3A4 metabolism of carbamazepine, diazepam,

paclitaxel, tamoxifen, midazolam, and terfenadine. Overall, the inhibitory effect of eribulin on CYP3A4 is unlikely to be clinically significant when the drug is co-administered with drugs known to be metabolized by this enzyme. The *in vitro* inhibition of eribulin metabolism by ketoconazole was not confirmed in the *in vivo* drug-drug interaction involving these two drugs [study 109].

- In study DDDA2008-004, eribulin was found to be a weak *in vitro* inhibitor of P-glycoprotein (P-gp) as the IC50 of eribulin on P-gp activity was estimated to be greater than 10 μM (i.e. > 7300 ng/mL eribulin free base). The mean efflux ratios of digoxin in the presence of 0.1, 1, 5, and 10 μM of eribulin to that of no eribulin were 1.1, 0.9, 0.7, and 0.5, respectively. These results suggest that the inhibitory effect of eribulin on P-gp observed *in vitro* is unlikely to be clinically significant.
- In study DMPKAM2010-003, eribulin was found not to inhibit CYP1A, CYP2B6, CYP2C9, CYP2C19, CYP 2D6, or CYP2E1 at IC_{50} concentrations > 200 μM (i.e., eribulin concentrations substantially greater than those expected in clinical use). The study also found that eribulin IC_{50} concentrations resulting in CYP3A4 inhibition against the probe substrates of midazolam, nifedipine, and testosterone were 2.21, 1.17, and 10.6 μM, respectively. The CYP3A4 results suggest that IC50 eribulin free-base concentrations ranged from ~ 730 to 7300 ng/mL. Consequently, the observed *in vitro* inhibitory effects of eribulin on CYP3A4 are unlikely to be clinically significant at plasma concentrations expected in clinical use.

  Comment: Eribulin at concentrations of up to 5 μM (i.e., up to 3650 ng/mL free base) did not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP2E1, but eribulin concentrations of 3 to 17 μM (i.e., 2190 to 12410 ng/mL free base) inhibited CYP3A4. Eribulin at concentrations up to 10 μM (i.e., up to 7300 ng/m free base) elicited minimal inhibitory effects on CYP3A4 mediated metabolism of carbamazepine, diazepam, paclitaxel, tamoxifen, midazolam, and terfenadine. Eribulin did not inhibit CYP1A, CYP2B6, CYP2C9, CYP2C19, CYP 2D6, of CYP2E1, with IC50 values for eribulin being greater than 200 μM for all enzymes. For CYP3A4, the IC50 values for inhibition by eribulin against the probe substrates of midazolam, nifedipine, and testosterone were 2.21 μM, 1.17 μM, and 10.6 μM, respectively (i.e., ~ 730 to 7300 ng/mL free base). *In vitro* data demonstrated that eribulin mediated CYP3A4 inhibition was reversible and competitive.

  There were no *in vivo* PK drug-drug interaction studies involving eribulin and drugs metabolized by CYP3A4. However, the *in vitro* data suggest that eribulin at clinically expected plasma concentrations is unlikely to significantly inhibit CYP3A4 activity. Nevertheless, the proposed PI recommends caution and monitoring when eribulin is co-administered with drugs that are mainly metabolized by CYP3A4, and precautions that concomitant use of eribulin with such drugs with a narrow therapeutic range should be avoided. The conservative approach in the PI to co-administration of eribulin and drugs metabolized by CYP3A4 is identical to that in the UK SPC. However, the US label adopts a more liberal approach, and indicates that eribulin is not expected to alter the plasma concentrations of drugs that are substrates of CYP3A4.

  Eribulin did not induce CYP1A or CYP3A at concentrations of 0.05 to 5 μM (i.e. up to 3650 ng/mL free base) or CYP2C9 or CYP2C19 at concentrations of 1 to 10 μM (i.e. up to 7300 ng/mL free base). Consequently, induction of CYP1A, CYP3A, CYP2C9 or CYP2C19 at relevant clinical concentrations of eribulin are unlikely. There was no statement in the PI reflecting these observations. However, the US label states that eribulin does no not induce CYP1A, CYP3A, CYP2C9 or CYP2C19 at relevant clinical concentrations.

  Ketoconazole (a potent CYP3A4 inhibitor) suppressed metabolism of eribulin (10 μM, 7300 ng/mL) *in vitro*, but the *in vivo* drug-drug interaction study showed that ketoconazole did not significantly increase exposure to eribulin. The PI states that no drug-drug interactions are expected with CYP3A4 inhibitors unless they are potent

inhibitors of P-gp. There is an identical statement in the UK SPC. The US label states that no drug-drug interactions are expected with CYP3A4 inhibitors or P-gp inhibitors.

Eribulin was found to be a weak *in vitro* inhibitor of P-gp, and is unlikely to inhibit this transporter protein at clinical relevant plasma concentrations. The *in vivo* PK interaction study between eribulin and ketoconazole (a potent CYP3A4 and P-gp inhibitor) did not result in increased eribulin exposure when the two drugs were co-administered.

There were no *in vitro* or *in vivo* drug-drug interaction studies with enzyme inducing substances and the PI includes a statement that co-administration of eribulin and such substances (e.g. rifampicin, carbamazepine, phenytoin, St John's Wort) should be avoided. Each of the listed substances is known to induce CYP3A4, and this enzyme has been shown to be the major enzyme involved in the metabolism of eribulin.

The PI states that there were no *in vitro* or *in vivo* studies with inhibitors of hepatic transport proteins such as organic anion transporting proteins (OATPs), P-glycoprotein (P-gp) (this is not strictly true as the submission included an *in vivo* drug-drug interaction study with ketoconazole which is not only a CYP3A4 inhibitor but also a P-gP inhibitor), and multidrug resistant proteins (MRPs). The absence of interaction data for co-administration of eribulin and inhibitors of hepatic transporting proteins is clinically relevant as up to 70% of a dose of eribulin is eliminated through biliary excretion. The PI and the UK SPC recommend against the co-administration of eribulin with substances which are inhibitors of hepatic transport proteins. The US label does not include such a warning. The sponsor's response to the EMEAs 120 questions states that two *in vitro* studies are being undertaken to investigate the uptake and inhibition effects of eribulin in several transporters using multidrug resistance protein (MRP), MRP2- or MRP4-expressing vesicles, breast cancer resistance protein (BCRP), organic cation transporter (OCT1), and organic anion transporter (OAT1, OAT3 or OATP1B1)- expressing cells.

4.2.4.3. Population-PK analysis

Inspection of the box and whisker plots in the population-PK analysis showed that co-administration of eribulin and CYP3A4 (n=29) inducers had no notable effect on eribulin clearance compared with eribulin alone (n=240). However, co-administration of eribulin and CYP3A4 inhibitors (n=7) reduced median eribulin clearance compared with eribulin alone (n=262), although the inter-quartile ranges (Q3-Q1) were similar for the two treatments. It is considered that little weight should be given to the population-PK CYP3A4 interaction analyses due to the marked imbalance in patient numbers between the two groups in both analyses.

4.3. Evaluator's overall conclusions on pharmacokinetics

The PKs of eribulin have been reasonably well characterized by the submitted studies, and there are no PK issues that should preclude approval of eribulin for the proposed indication.

The population-PK study demonstrated that the best final PK model for eribulin was a three compartment model with linear elimination. Following iv administration, eribulin undergoes a rapid distribution phase followed by a prolonged elimination phase with a terminal half-life of about 42 hours. The drug has a large volume of distribution with the range of means (Vss) from the Eisai sponsored PK studies being 41.0 to 114.2 L/m^2. The drug undergoes minimal preferential distribution from the plasma into red blood cells. Protein binding is low ranging from ~49% to ~65%, and is independent of eribulin concentration from 100 to 1000 ng/mL.

There was no formal dose proportionality study in the submission. However, pooled data from the three Eisai dose escalation studies showed that eribulin exposure (AUC) increased with dose over the range 0.25 to 4.0 mg/m^2. In addition, the data showed that CL, t½ and Vss were independent of dose, confirming that the PKs of eribulin were linear. The PKs of eribulin following the 2nd or 3rd weekly dose in the first cycle were similar to the PKs following the 1st

dose, and no accumulation occurred after repeat dosing at weekly intervals. The population-PK study reported high inter-individual variance for both the clearance and volume of distribution (central compartment) of eribulin with the respective coefficients of variation (CV) being 45.6% and 42.3%. High intersubject variability in the PKs of eribulin were also observed in those individual PK studies in which the proposed eribulin dose of 1.4 mg/m^2 was administered.

Following iv administration of ^{14}C-eribulin, unchanged eribulin accounted for over 90% of the entire drug-derived radioactivity in the plasma, indicating that only low levels of circulating metabolites are formed. No major metabolites were found in the plasma and metabolite concentrations represented ≤ 0.6% of parent eribulin. *In vitro* data demonstrated that CYP3A4 was the main enzyme responsible for the metabolism of eribulin, and that the metabolites formed by this enzyme were mainly the isomeric monohydroxylates.

Following administration of ^{14}C-erubulin ~90% of the radioactivity was recovered (~82% in the faeces and ~9% in the urine). Unchanged eribulin accounted for ~88% and ~91% of the total radioactivity excreted in the faeces and urine respectively. Overall, the results suggest that eribulin is primarily eliminated unchanged by biliary excretion. In the mass balance study, eribulin total clearance was 3.93 L/h, and the renal clearance of 0.301 L/h represented less than 10% of total clearance. The actual renal clearance of ~0.3 L/h is very low compared with the fraction of eribulin unbound in plasma x the glomerular filtration rate (i.e. ~0.6 x 7.5 L/hr = 4.5 L/hr). This suggests that eribulin is reabsorbed in the kidneys and may be secreted (but to a lesser extent than it is reabsorbed). If it is assumed that the non-renal clearance of ~3.6 L/h approximates hepatic clearance (CLH) then it can be estimated that the hepatic extraction ratio (EH) is 0.04 (i.e. CLH = QH x EH; where QH is hepatic blood flow of 90 L/hr). The low hepatic extraction ratio is consistent with the long terminal half life of eribulin.

The population-PK study found that eribulin clearance increased with increasing body weight, and there was also a strong trend for increasing body weight to be associated with increasing volume of distribution. In addition, this study found that albumin, bilirubin and alkaline phosphatase levels were predictors of eribulin clearance. Clearance decreased with increasing levels of bilirubin and alkaline phosphatase, and increased with increasing levels of albumin. The population-PK study demonstrated that age, gender, race, and co-administration of CYP3A4 inducers and inhibitors were not important predictors of eribulin clearance.

Hepatic impairment increases exposure to eribulin with the $AUC_{0-\infty}$ being ~1.8 and ~2.8-fold greater in patients with mild hepatic impairment (Child-Pugh A) and moderate hepatic impairment (Child-Pugh B), respectively, than in patients with normal renal function. Consequently, downward dose adjustments are recommended to 0.7 mg/m^2 for patients with moderate hepatic impairment and 1.1 mg/m^2 for patients with mild hepatic impairment. There are no satisfactory data on the PKs of eribulin in patients with severe hepatic impairment.

Renal impairment increases exposure to eribulin, despite renal excretion of unchanged eribulin being less than 10% of an administered dose. Unconfirmed data are reported to show that the mean geometric dose normalized exposure increases 2-fold in patients with moderate renal impairment (CrCL 30-50 mL/min). Consequently, it is recommended that the dose be adjusted downwards to 1.1 mg/m^2 in patients with moderate renal impairment. No dose adjustment is recommended for patients with mild renal impairment (CrCL 50-80 mL/min). There are no data on the PKs of eribulin in patients with severe renal impairment (i.e., CrCL < 30 mL/min).

In a PK drug-drug interaction study, co-administration of eribulin and ketoconazole (a potent CYP3A4 inhibitor and a P-gp inhibitor) did not increase eribulin exposure compared with eribulin alone. The submitted data indicate that a drug-drug interaction study with the CYP3A4 inducer rifampicin commenced after the data cut-off date for the submission. *In vitro* studies have shown that eribulin is unlikely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP 2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4, or induce CYP1A, CYP3A, CYP2C9, or CYP2C19 at clinically expected plasma concentrations. *In vitro* studies show that eribulin is a weak inhibitor of P-gp,

but this effect is unlikely to be significant at clinically expected eribulin concentrations. The sponsor indicates that *in vivo* studies are being undertaken to investigate the uptake and inhibitory effects of eribulin in several protein transporter systems. These investigations are considered to be clinically important as it has been estimated that up to 70% of an administered dose of eribulin is eliminated through biliary excretion.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The submission included four studies in patients with advanced solid tumours with PK/PD data, one of which also included secondary pharmacology data on the effect of eribulin on the QTc interval. Table 14 lists the relevant studies. There was also a PK/PD (and PK/AE) report using pooled data from the Phase II study [211].

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration. There were no pharmacodynamic studies in healthy human volunteers. There were no studies in humans on the primary pharmacology of eribulin.

Table 14: Submitted clinical pharmacokinetic studies; n = subjects entered / evaluated.

Identification	Primary Aim	n
E7389-A001-101 E7389-A001-102 E7389-J081-105	MTD; PK/PD (C_{max}, and AUC / ANC and fatigue). MTD; PK/PD (C_{max} and AUC / ANC and fatigue). MTD.	33 / 32 21 / 21 15 / 15
E7389-E044-110	QTc interval	26 / 23
Population PK/PD [and PK/AE] Report (Pooled Data from Phase II study 211)		211

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Relationship between drug concentration and PD effects

5.2.2. PK/PD analysis dose escalating studies

- In study 101 (advanced solid tumours), eribulin was administered on Days 1, 8, and 15 every 28 days (1 cycle) to 5 cohorts at doses of 0.25 (n=2), 0.5 (n=7), 0.7 (n=4), 1.0 (n=9), and 1.4 (n=9) mg/m^2. The maximum tolerated dose (MTD) was 1.0 mg/m^2. The MTD was defined as the highest dose at which no more than 1/6 patients evaluable for toxicity experienced dose limiting toxicity (DLT). A PK/PD analysis was performed to explore the relationship between absolute neutrophil count (ANC) and fatigue with eribulin exposure. Two approaches were used: a PK/PD analysis of the ANC response as a continuous variable using an inhibitory E_{max} model and a logistic regression analysis using the Common Toxicity Criteria (CTC) grade of ANC . The latter method was also employed to model fatigue. The

incidence of neutropenia (but not fatigue) as a component of the dose-limiting toxicities (DLTs) was demonstrated to depend on drug exposure. From the analysis of the ANC as a continuous variable, for C_{max} and $AUC_{0-\infty}$ the PK/PD relationship was best described by simple and sigmoidal inhibitory E_{max} models, respectively. Typical exposures at which the ANC decreased by 50% were estimated to be 187 ng/mL (RSE ± 28%) for the C_{max}, and 824 ng.hr/mL (RSE ± 18%) for the $AUC_{0-\infty}$.

- In study 102 (advanced solid tumours), eribulin was administered on Day 1 of a 21-day cycle to 6 cohorts at doses of 0.25 (n=1), 0.5 (n=4), 1.0 (n=3), 2.0 (n=7), 2.8 (n=3), and 4.0 (n=3) mg/m^2. The MTD was 2.0 mg/m^2, and was defined as the highest dose at which no more than 2/6 patients evaluable for toxicity experienced DLT. A PK/PD analysis was performed to explore the relationship between ANC and fatigue with eribulin exposure using the same analytical methods as those in study 102. The incidence of neutropenia (but not fatigue) as a component to the DLTs seen in this study was demonstrated to depend on drug exposure. From the analysis of ANC as a continuous variable, for C_{max} and $AUC_{0-\infty}$, the PK/PD relationship was best described by a sigmoidal inhibitory E_{max} model. Typical exposures at which the ANC decreased by 50% were estimated to be 117 ng/mL (RSE ± 15%) for the C_{max} and 396 ng.hr/mL (RSE ± 22%) for the $AUC_{0-\infty}$.

- In study 105 (Japanese patients with advanced solid tumours), eribulin was administered on Days 1 and 8 of a 21-day cycle to 4 cohorts at doses of 0.7 (n=3), 1.0 (n=3), 1.4 (n=6), and 2.0 (n=3) mg/m^2. In this study, it was estimated that the MTD was 2.0 mg/m^2 and the recommended dose for Phase II studies was 1.4 mg/m^2. DLTs were observed in 2/6 patients at the 1.4 mg/m^2 dose and 3/3 patients at the 2.0 mg/m^2 dose. In this study, C_{max} and AUC_{0-t} values were strongly correlated with the rates of decrease in neutrophil count and white blood cell count ($R^2 > 0.5$).

  Comment: In studies 101 and 102, respective typical exposures at which the ANC decreased by 50%, an index of drug sensitivity, were estimated to be 187 ng/mL (RSE ± 28%) and 117 ng/mL (RSE ± 15%) for the C_{max} and 824 ng.hr/mL (RSE ± 18%) and 396 ng.hr/mL (RSE ± 22%) for the $AUC_{0-\infty}$. In study 101, the mean (CV%) C_{max} and $AUC_{0-\infty}$ Day 15 values for eribulin were 247 (14%) ng/mL and 913 (76%) ng.hr/mL, respectively. The MTD was estimated to be 1.0 mg/m^2 in study 101 and 2.0 mg/m^2 in studies 102 and 105 (with the recommended dose for Phase II studies in Japanese patients with solid tumours being 1.4 mg/m^2 based on the data from study 105).

5.2.3. Population-PK report

5.2.3.1. Population PK/AE analysis

The objective of the population PK/AE analysis was to develop three separate models linking exposure to the probability of a patient experiencing Grade 4 neutropenia, Grade ≥ 3 fatigue or asthenia, or Grade ≥ 3 neuropathy. Only the data from the Phase II study 211 were used for the PK/AE evaluation. Study 211, was an open-label, single-arm, multicentre, Phase II study that investigated the efficacy, safety, and PK of eribulin in 299 patients with metastatic or locally advanced breast cancer. Patients were required to have previously been treated with 2 to 5 chemotherapy regimens (including an anthracycline, a taxane, and capecitabine) with documented progression on or within 6 months of last chemotherapy. Patients were administered eribulin at a dose of 1.4 mg/m^2 given iv over 2-5 minutes on Days 1 and 8 of a 21-day cycle. Sparse PK sampling was used in this study. Four blood samples were drawn during Cycle 1 between 5 minutes and 120 hours after the first dose. PK data were available from a total of 211 patients.

The final database used for PK/AE model building and evaluation consisted of 1050 observed AE records from 211 patients who had individual PK parameter estimates. Therefore, there were 100% of the original AE observations and 100% of the original patients available for

evaluation. AE data were fitted using Nonmem software using an ordered categorical logistic regression approach. Model building and covariate assessments were conducted using standard methods for each AE type. The final models for the PK/AE assessments were evaluated for performance using several standard tests, including nonparametric bootstrapping and graphical assessment. A summary of baseline patient characteristics in the PK/AE model building database is provided in Table 15.

Table 15: Baseline patient data for AE model building database (n=211).

Demographic/Covariate (unit)	Mean (SD)	Median	Range (Min-Max)
Age (y)	56.22 (11.11)	57	27-81
Weight (kg)	67.84 (13.95)	65.9	40.9-122
Height (cm)	162 (6.76)	163	146-180
BSA (m^2)	1.72 (0.17)	1.7	1.31-2.36
Albumin (g/dL)	3.78 (0.50)	3.84	2-4.78
Alkaline Phosphatase (IU/L)	171 (157)	116	27-1052
Alanine Transaminase (IU/L)	38.15 (38.76)	28	5-343
Aspartate Transaminase (IU/L	45.07 (34.87)	34	7-237
Bilirubin (mg/dL)	0.58 (0.40)	0.48	0.16-4.53
Total Protein (g/dL)	7.01 (0.67)	7	4.8-9.5
Creatinine Clearance (mL/min)*	90.17 (31.42)	86.8	36.8-197
RBC (cells x 10^9)/L	3.90 (0.48)	3.88	2.57-5.4
Dose (ug)	2126 (282)	2091	884-4420
AUC (ug.h/L)	851 (554)	712	213-5118
Cmax (ug/L)	498 (197)	479	91.3-1918
Number of Cycles	4.98 (3.56)	4	1-27
ECOG	0=68; 1=132; 2=11		
Race	Caucasian=136; Black=16; Asian (non Japanese, Pacific Islander)=4; Japanese=0; Hispanic=0; Native American=0; Other=4; Missing=51		

* CrCl capped at 150 mL/min as the upper limit.

Fatigue - Eribulin exposure (measured by Dose, C_{max}, and AUC) was not a predictor of fatigue. The probability of a Grade 3 fatigue was very low in all patients. When evaluated as an ordered categorical logistic model, the best predictor for the probability of fatigue was stratified ECOG performance status (ECOG 0 and 1 vs. ECOG 2 and 3) with an effect of cycle on patients with ECOG status of 0 or 1.

Neuropathy - When evaluated as an ordered categorical logistic model, the best model describing the probability of neuropathy used AUC multiplied by cycle number to predict the likelihood of neuropathy. The probability of a patient experiencing Grade 3 neuropathy appeared to be cumulative with the probability being low in the first cycle of treatment (less than 0.1%) regardless of the eribulin AUC and slowly increasing with increasing treatment cycles at higher exposures. For an eribulin AUC value of 500 µg.h/L, the calculated probability of a Grade 3 neuropathy was less than 1% for up to 10 cycles of treatment. However, for an AUC value of 2500 µg.h/L, the calculated probability of Grade 3 neuropathy reached 0.990% at Cycle 6, and 1.34% at Cycle 10. The use of Dose as an explanatory covariate for the probability of neuropathy gave similar predictive performance when compared with AUC which suggests that evaluations of the probability of neuropathy can be conducted in patients who do not have pharmacokinetic data. C_{max} and AUC alone were not predictors of neuropathy. No other covariates, including age, gender, or race, were identified as being predictive of the probability of experiencing neuropathy.

Neutropenia – When evaluated as an ordered categorical logistic model, the best predictor for neutropenia was AUC, with AST as a power function. The probability of experiencing Grade 4 neutropenia over a range of eribulin exposure values (500-2500 µg.hr/L) ranged from 4% to 13% for patients with normal AST (AST=40 IU/L), from 7% to 25% for patients with elevated AST levels of 100 IU/L, and from 13% to 35% for patients with elevated AST levels of 200 IU/L. There was no evidence of cumulative toxicity with regards to neutropenia. For neutropenia, the shrinkage for the model was 0.259 suggesting that the probabilities based on the AUC and AST

reasonable. However, Dose and C_{max} were not good predictors of the probability of a patient experiencing neutropenia.

Comment: The data suggesting that the best predictor of developing Grade 3 neuropathy was the AUC multiplied by the cycle number should be interpreted with caution. The shrinkage for the relevant neuropathy model was high (0.462) suggesting that the model is over parameterized for the amount of information contained in the data (i.e., there are too few individuals with Grade 3 neuropathy to provide an unbiased assessment of the parameter estimate [i.e., AUC x cycle number]). One of the problems with population analysis is the tendency of the individual parameter estimates to "shrink" towards the mean value. This shrinkage is usually associated with too little data from each individual to provide a robust estimate of the parameter of interest. Small values for shrinkage (less than approximately 0.2) indicate good individual estimates of the parameter of interest, while large values indicate poor individual estimates of the parameter of interest. Therefore, based on a shrinkage of 0.46 the data from the relevant model should be interpreted with caution as the results are likely to be unreliable. The database for Grade 3 neuropathy showed that while there was an overall incidence of Grade 3 neuropathy of 6.16%, there were no patients with a Grade 3 event in cycles 1 or 2, one subject had an event in cycle 3, 5 patients had a Grade 3 in cycle 4, and 4 patients had a Grade 3 event in cycle 5. Consequently, the raw data indicate that in the first few cycles of treatment a Grade 3 neuropathy event is unlikely and that the probability of a patient experiencing this event in any given cycle is low.

The probability of patients experiencing Grade 4 neutropenia is related to eribulin AUC and AST. Patients with high AST (potentially indicating poor hepatic function) appear to be more likely to experience Grade 4 neutropenia than patients with normal AST levels. Exposure to higher eribulin AUC results in a proportionally greater probability of Grade 4 neutropenia. Eribulin exposure was not a predictor of fatigue.

5.2.4. Population PK/PD (outcome) evaluation

The objective of the PK/PD evaluation was to conduct an exploratory graphical assessment of the possible relationships between eribulin exposure (AUC) and measures of clinical outcome (tumour response and survival). Only data from the patient population in Study 211 were included in this analysis and these data were used to graphically correlate response to treatment. As the PK/PD evaluation was to be an exploratory graphical assessment, only the AUC from the first dose was used to evaluate the clinical response. The AUC data used in the evaluation was either continuous or quartile (i.e., categorical) depending on the analysis (i.e., Q1 AUC < 499.2; Q2 499.2 ≤ AUC < 712.4; Q3 712.4 ≤ AUC < 90.05; Q4 ≥ 980.05). Clinical response data were obtained throughout the course of therapy. There were no patients judged as being complete responders in this database.

The objective response rates versus AUC quartile showed a slight decrease as exposure increased. However, the confidence intervals were wide. Box and whisker plots of AUC (continuous) versus best recorded response showed no notable differences between exposure and progressive disease, partial response, and stable disease. Kaplan-Meier plots suggested that patients with higher exposures (AUC quartiles) may have shorter times to progression. However, there was substantial overlap of 95% confidence intervals around each of the Kaplan-Meier fits and substantial overlap between the bands for the AUC quartiles. In the Kaplan-Meier plots there were anomalies in patient classification relating to disease progression which make the data unreliable. In the overall survival analysis there was a trend towards longer survival with lower AUC, but once again there was substantial overlap of the 95% confidence intervals around each of the Kaplan-Meier fits, and overlap between the bands for the AUC quartiles.

Comment: The PK/PD analysis was exploratory based only on various graphical assessments of the relationship between clinical outcomes and eribulin exposure defined

by AUC levels. There were no statistical analysis or model building relating to PK/PD (outcome) relationships. It is considered that no clinically meaningful conclusions relating to exposure and outcomes can be made based on the interpretation of the graphical assessments. There were methodological problems relating to patient misclassification and/or failure to account for patient dropouts.

5.2.5. Special study relating to the QT interval [study 110]

Study 110 was an open-label, multicentre, single arm study of the effects of eribulin on QT interval prolongation in patients with advanced solid tumours. The primary objective of the study was to assess whether eribulin has an impact on the ECG with focus on cardiac repolarization, as measured by the QT/QTc interval as well as through a PK/PD analysis. Treatment consisted of eribulin 1.4 mg/m^2 administered as an iv bolus over 2-5 minutes or diluted in up to 100 ml 0.9% NaCl for iv infusion over 2-5 minutes on Days 1 and 8 of the first 21-day cycle. Patients who demonstrated clinical benefit without significant toxicity could continue treatment in subsequent cycles.

The primary end point of interest was the largest mean difference between the time-matched baseline QTcF and the post-dosing QTcF, considering all post-treatment assessments on Day 1 and Day 8. QTcF values on both days were baseline-adjusted by subtracting values recorded on the day before the first dose (Day -1) at the same nominal timepoints (i.e., time-matched ΔQTcF). Multiple ECGs and PK samples were collected at Baseline, and on Day 1 and Day 8. The sample size for the study was primarily based on feasibility considerations. However, it was estimated that a sample of 22 patients would ensure an 80% power when mean QTcF change from baseline was 10 milliseconds (msec), with a standard deviation of 18 msec.

5.2.5.1. ECG Results

A total of 910 digital 12-lead ECGs and 2757 ECGs extracted from Holter recordings were included in the analysis. The 12-lead ECG Holter/digital results for the Day 1 and Day 8 mean and one-side 95% CI of the baseline-adjusted time matched ΔQTcF in the per-protocol population are summarised below in Table 16. On Day 1, QTcF mean [upper 95% CI] changes from the time matched baseline post-dose ranged from -6 [6.2] to 2 [5.1] msec, and the lowest and highest values occurred at the 24 hour and the 15 minute time points, respectively. The mean [upper 95% CI] change from baseline pre-dose time matched QTcF on Day 1 was 4 [7.3] msec. The upper 95% CI for all mean baseline-adjusted QTcF post-dose time points was ≤ 8 msec. On Day 8, QTcF mean changes from baseline were larger than on Day 1 and the variability substantially higher, resulting in wider confidence intervals. QTcF mean [upper 95% CI] changes from pre-dose baseline to post-dose at all time points on Day 8 ranged from 3 [9.7] msec at 5 hours post-dose to 11 [17.2] msec at 6 hours and 11 [19.5] msec at 15 minutes post-dose. The highest upper 95% CI for all mean baseline-adjusted time-matched ΔQTcF post-dose was 19.5 msec at 15 minutes post-dose.

Table16: Mean and one-side 95% CI of QTcF change from baseline vs time profile: per-protocol population.

	Day 1			Day 8		
Time (hours)	N	Mean (SD) QTcF (msec)	Upper 95% CI	N	Mean (SD) QTcF msec	Upper 95% CI
0	23	4 (8.8)	7.3	20	9 (19.3)	17.9
0.08	26	0 (12.5)	5.1	22	6 (16.1)	12.9
0.25	26	2 (12.3)	6.7	23	11 (18.7)	19.5
0.5	26	0 (14.0)	5.7	23	8 (20.5)	17.0
1	26	0 (13.1)	5.1	23	7 (16.5)	14.0
1.5	25	-1 (12.0)	4.4	22	5 (16.1)	11.8
2	24	0 (13.6)	5.8	22	7 (17.5)	14.8
3	25	-1 (9.9)	3.2	23	10 (18.0)	17.9
4	24	1 (12.8)	6.7	22	9 (20.2)	18.2
5	26	-2 (9.6)	2.1	23	3 (16.3)	9.7
6	26	1 (9.1)	4.6	23	11 (14.7)	17.2
10	25	0 (19.6)	8.0	22	8 (17.3)	15.6
24	26	-6 (20.1)	2.5	23	8 (18.8)	16.5
48	26	-2 (20.0)	6.2	23	4 (19.1)	12.4

On Day 1, there were no patients with QTcF intervals of 470-500 msec or >500 msec. On Day 8, one patient had a QTcF of 470-500 msec at several post-dose time-points (treatment was not discontinued), and no patients had a QTcF > 500 msec. The time-matched QTcF change from baseline was also analyzed in an *ad hoc* analysis by gender. On Day 8, the time-matched QTcF change from baseline varied between 9 msec and 18 msec in women (n=10-11) and between -2 msec and 7 msec in men (n=10-12). As expected, the observed QTcF prolongation was larger in women.

On Day 1, there was no apparent time-dependent pattern in the numbers of patients with changes from baseline in QTcF for time-matched Holter ECG Results. Between 8 (30.8%) and 17 (65.4%) patients had a change from baseline in QTcF of > 0 to ≤ 30 msec at any time-point during the period of 15 minutes to 48 hours post-dose, and 5 patients had a change of >30 to ≤ 60 msec during the same period. None of the patients with a QTcF change of > 30 to ≤ 60 msec discontinued the study or had their eribulin dose reduced for the second infusion at Day 8 due to this change.

On Day 8, there was no apparent time-dependent pattern in the numbers of patients with changes from baseline in QTcF for time-matched Holter ECG Results. Between 10 (43.5%) patients and 15 (65.2%) patients had a change from baseline in QTcF of > 0 to ≤ 30 msec at any time-point during the period of 15 minutes to 48 hours post-dose. A total of 10 patients had changes from baseline in QTcF of > 30 to ≤ 60 msec post-infusion during the same time period (i.e., twice the number of patients on Day 1). There was 1 patient who had a change from baseline in QTcF of > 60 msec (i.e., 65 msec) which occurred at 4 hours post-dose.

No significant changes in the QRS and PR intervals were observed. However, on both Day 1 and Day 8, an initial reduction from baseline in the heart rate of up to 5-6 beats per minute was observed during the first 1.5 hours after eribulin administration, which then returned to baseline levels by about 3-6 hours. The sponsor speculates that this may have been caused by differences in physical activity or autonomic tone (induced, as an example by nausea) between the baseline and treatment days.

5.2.5.2. Pharmacokinetic results

The PK parameters on Day 1 and Day 8 are summarised in Table 17 . The PKs on both days were almost identical, and visual inspection of the plasma concentration time versus time curves showed them to be superimposable. The protocol planned to estimate the $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2,z}$, CL and V_{ss}. However, as the PK sample collection was 0 to 48 hours and the terminal elimination half-life of eribulin is ~40 hours, the $AUC_{0-\infty}$, $t_{1/2,z}$, CL and V_{ss} could not be estimated.

Table 17: Mean PK parameters on Day 1 and Day 8; PK population.

Parameter	Cycle 1, Day 1 Mean (SD)	Cycle 1, Day 8 Mean (SD)
N	26	23
Actual data		
C_{max} (ng/mL)	516.5 (137.91)	502.4 (138.31)
t_{max} (hr)	0.08 (0.07 – 0.25)	0.08 (0.05 – 0.25)
$AUC_{(0\text{-}48\ hrs)}$ (ng.hr/mL)	628.1 (257.68)	629.1 (235.53)
Dose-normalized data		
C_{max} (ng/mL/mg)	239.6 (69.12)	234.3 (77.48)
$AUC_{(0\text{-}48\ hrs)}$ (ng.hr/mL/mg)	294.7 (133.54)	296.1 (138.86)

Note: Data are shown as mean (SD), except for tmax which are median (range).

5.2.5.3. PK/PD analysis

In a PK/PD analysis, the relationship between QTcF and eribulin concentration was assessed using linear mixed effect modelling to estimate the maximal change (mean, and upper 95% CI) in the baseline adjusted QTcF. The model predicted that the Day 8 average ΔQTcF was higher (7.55 msec) than the Day 1 average ΔQTcF (-0.35 msec), although there was no difference between Day 1 and Day 8 in the mean eribulin plasma concentrations. Modelling showed no statistically significant relationship between QTcF and eribulin concentrations.

> **Comment:** The Day 8 data give rise to "regulatory concern" as the maximum post-dose time-matched QTcF prolongation was > 5 msec and the maximum upper bound of the 95% CIs was > 10 msec (see relevant TGA adopted EU Note for Guidance [CHMP/ICH/2/04] with Australian specific amendment). Furthermore, the Day 8 baseline-adjusted time-matched data showed greater QTcF prolongation in women compared with men, and there was no QTcF prolongation study specifically in women. Overall, the QTcF data support the inclusion of a precautionary statement in the PI.
>
> The study found that the post-dose baseline-adjusted time-matched QTcF intervals were greater on Day 8 than on Day 1. The Day 1 ΔQTcF intervals were ≤ 2 msec and the upper 95%CI was ≤ 8 msec at all post-dose time-points. These results suggest that eribulin mesylate at the proposed dose did not significantly prolong the QTcF interval on Day 1. However, on Day 8 the maximum time-matched post-dose change in the QTcF interval was 11 msec which occurred at 15 minutes and 6 hours. In addition, the maximum upper 95% CI for the time-matched post-dose change in the QTcF interval was 19.5 msec which occurred at 15 minutes. The categorical QTcF data also showed that changes in the QTcF interval were more marked on Day 8 than Day 1.
>
> The PKs of eribulin were almost identical on Day 1 and Day 8, and the PK/PD analysis showed that the increase in the QTc interval on Day 8 was unrelated to plasma eribulin concentration. Reassuringly, no AEs relating to the ECG were reported during the study. Four patients experienced 5 AEs of interest (presyncope [2 events], tachycardia, vertigo and atrial fibrillation). The vasovagal episodes and presyncopes reported could not be attributed to a proarrhythmic event. All QTc values at any time associated with AEs were below 450 msec, and all events were considered to be unrelated to study drug. The reason for the Day 8 increase in the QTc compared with Day 1 are unknown. However, the sponsor speculates that although a "delayed drug effect can not be excluded ....other factors such as nausea, vomiting, diarrhea, and electrolyte disturbances may have caused or contributed to the small, observed QTc prolongation".
>
> The submission included an additional analysis of the QT interval using the QTcNi (i.e., individually-based correction of QTc). The increase in the QTc interval was smaller when the QTcNi was applied than that observed when the QTcF was applied. Consequently, the sponsor suggested that the QTcF was not the most appropriate correction method for

heart rate in the particular study population. Nevertheless, the time-matched ΔQTcNi values were still greater on Day 8 than Day 1. Furthermore, on Day 8, the greatest mean time-matched ΔQTcNi value was 9 msec at 6 hours and the highest upper 95% CI was 15.8 msec at 4 hours. Consequently, although the Day 8 ΔQTcNi values were smaller than the Day 8 ΔQTcF values the results still gives rise to "regulatory concern".

It is noted that the submitted QT study did not comply with the relevant TGA adopted guidelines for such studies (i.e., EU Note for Guidance [CHMP/ICH/2/04] with Australian specific amendment). The relevant guidance document states that a "thorough QT/QTc study" should be "adequate and well controlled, including randomisation, appropriate blinding, and concurrent placebo-control". The sponsor acknowledges that the submitted study was not a "thorough QT/QTc study" [TQT]. However, the sponsor states that "a standard ...TQT study cannot be carried out with a cytotoxic agent and thus Study 110 was designed to meet the alternate pathway per ICH E14" [i.e. the relevant TGA adopted guidance document but without the Australian specific amendment], and provides supportive arguments based on similarities between the features of the submitted study and those of a TQT study (sponsor's response to EMEA 120 day question). These features included: a carefully selected ECG schedule to ensure that the peak plasma concentration of eribulin was captured; continuous, digital, high-frequency 12-lead ECG recordings during a full baseline day and on Day 1 and Day 8 in the first treatment cycle; extraction of ECG recordings pre-infusion and at several time points post-infusion on Day 1 and Day 8 and at corresponding clock times during the baseline day; stringently controlled experimental conditions with patients supinely resting around time points of ECG extraction on all study days (Days 0, 1 and 8); blood samples drawn after each ECG extraction time window; extraction of high-quality ECG strips in triplicate by a central ECG laboratory; ECG interval measurements using a validated technique by the central ECG laboratory; and calculation of time-matched change-from-baseline at each time point after the eribulin infusion. In addition, the sponsor provided a satisfactory justification for the lack of a positive control. Overall, it is considered that the sponsor's justification for no submitting a TQT study in this patient population with advanced solid tumours is acceptable.

5.3. Evaluator's overall conclusions on pharmacodynamics

The dose-escalation studies 101 and 102 demonstrated that reductions in the ANC were related to increased exposure to eribulin, and the population-PK study showed that the probability of experiencing a Grade 4 neutropaenia was related to increased eribulin exposure (AUC) and increased AST levels. It is considered that the available PK/AE data suggest that the increased risk of experiencing reductions in the ANC and increases in Grade 4 neutropenia can be expected at clinically relevant eribulin exposures. The available PK/AE do not establish a relationship between increasing eribulin exposure and fatigue or neuropathy. In addition, the exploratory PK/PD data do not establish a relationship between eribulin exposure and clinical outcomes such as overall survival and disease progression.

The data from the QT interval study [110] is considered to give rise to "regulatory concern" as, following a dose of eribulin 1.4 mg/m^2 on Days 1 and 8, the Day 8 maximum post-dose time-matched QTcF prolongation was > 5 msec, and the maximum upper bound of the post-dose time-matched 95% confidence interval was > 10 msec. Furthermore, the increase in QTcF on Day 8 was greater in women than in men (an expected finding). The PKs of eribulin were almost identical on Day 1 and Day 8, and the PK/PD analysis showed that the increase in the QTc interval on Day 8 was unrelated to plasma eribulin concentration.

6. Dosage selection for the pivotal studies

The eribulin dose of 1.4 mg/m^2 (administered as an iv bolus over 2 to 5 minutes on Days 1 and 8 of each 21-day cycle) was selected from experience in the Phase I/II studies. In the first Phase I dose-finding study [NCI 5730], the MTD was determined to be 1.4 mg/m^2 in patients with advanced solid tumours when administered as a bolus on Days 1, 8, and 15 of a 28 day cycle. Based on these results, an eribulin dose regimen of 1.4 mg/m^2 administered as an iv bolus on Days 1, 8, and 15 of a 28-day cycle was chosen for further exploration in two, Phase II, open-label, single-arm studies [201, 202]. Following these two studies, the eribulin dose regimen of 1.4 mg/m^2 iv bolus on Days 1 and 15 of a 21-day cycle was chosen for the Phase III study [305].

Study 201 included patients with advanced metastatic breast cancer previously treated with chemotherapy including an anthracycline and a taxane. In the first cohort (n=71), patients received eribulin 1.4 mg/m^2 iv bolus on Days 1, 8, and 15 of a 28-day cycle. However, because of the high number of dose delays, reductions or omissions due to neutropenia on Day 15, a second cohort (n=33) was added to receive 1.4 mg/m^2 iv bolus on Days 1 and 8 of a 21-day cycle. In this study the primary endpoint was the overall response rate (complete response [CR] or partial response [PR], confirmed 4 to 8 weeks after first observed). The efficacy analysis showed that in the 28-day schedule cohort 11.5% (10/87) of patients were assessed with PR as best response compared with 14.3% (4/28) of patients in the 21-day cohort. There were no patients in the study with CR. Dose interruptions, delays or omissions were reported in 76% of patients in the 28-day schedule group and 42% of patients in the 21-day schedule group. The 1.4 mg/m^2 dose regimen on Days 1 and 8 of a 21-day cycle was considered to have an acceptable tolerability profile, with neutropenia, fatigue, and alopecia being the most common treatment-related AEs.

Study 202 included patients with advanced non-small cell lung cancer (NSCLC) who had progressed during or after initial treatment with platinum-based doublet chemotherapy stratified for prior taxane therapy. In this study, it was initially planned to have a group of patients (taxane pre-treated and taxane-naïve patients) treated with eribulin 1.4 mg/m^2 iv bolus on Days 1, 8, and 15 of a 28-day cycle. However, after a preliminary evaluation of data from the first 33 patients in the 28-day cohort, it was noted that 17 patients had missed the Day 15 dose due to haematological toxicity. The haematological toxicity seemed to have recovered by Day 21 in most cases. Efficacy outcomes were similar between those patients who had received the Day 15 dose and those who had not received the Day 15 dose. These findings led to a protocol amendment resulting in the addition of a second dosing schedule cohort in which eribulin was administered as a 1.4 mg/m^2 iv bolus on Days 1 and 8 of a 21-day cycle to evaluate the efficacy and safety of this alternate dose schedule. A total of 106 patients were enrolled, 78 patients (58 taxane pre-treated and 20 taxane-naïve patients) treated with eribulin 1.4 mg/m^2 iv bolus on Days 1, 8, and 15 of a 28-day cycle, and 28 taxane pre-treated patients treated with eribulin 1.4 mg/m^2 iv bolus on Days 1 and 8 and of a 21-day cycle. Differences in efficacy were observed between the two cycles, with patients in the 28-day cohort having a PR rate of 11.7% and a disease control rate of 59.7%, compared with a PR rate of 3.8% and a disease control rate of 42.3% in patients in the 21-day cohort. Grade 3-4 hematological toxicity (anaemia, leukopenia, and neutropenia) was more frequently observed in patients in the 21-day cohort compared with patients in the 28-day cohort. However, Grade 3-4 nausea, fatigue, pyrexia, and dehydration were more frequently observed in the patients in the 28-day cohort compared with the 21-day cohort.

> **Comment:** The data from the two Phase II studies [201, 202] indicate that the 1.4 mg/m^2 iv bolus dose regimen administered on Days 1 and 8 of a 21-day cycle was appropriate for further investigation in the supportive Phase II study [211] and the pivotal Phase III study [305] in patients with locally recurrent or advanced or metastatic breast cancer previously treated with chemotherapy.

7. Clinical efficacy

7.1. Pivotal efficacy study [study 305]

7.1.1. Study design, objectives, locations and dates

The *pivotal study* was a Phase III, multi-national (19 countries), multi-centre (135 centres), open-label, randomised, 2-group trial comparing the effects of eribulin with Treatment of Physician's Choice (TPC) in patients with locally recurrent or metastatic breast cancer previously treated with chemotherapy. The study is also known by the acronym EMBRACE (i.e., **E**isai **M**etastatic **Br**east Cancer Study **A**ssessing Physician's **C**hoice Versus **E**7389). The results of the EMBRACE study have been published.[3] Eribulin mesylate (also identified as E7389) will be referred to as eribulin in the review of evaluation of study 305.

The *primary objective* of the pivotal study was to compare eribulin with TPC on overall survival (OS) in patients with locally recurrent or metastatic breast cancer who had received 2 to 5 prior chemotherapy regimens, which must have included an anthracycline and a taxane, and at least 2 of which must have been given for locally recurrent or metastatic disease. Patients must also have been refractory to their latest chemotherapy regimen, documented by progression on or within 6 months of therapy. Human epidermal growth factor receptor 2 (HER2/*neu*) positive patients could have received trastuzumab in centres where this treatment was available, and estrogen receptor (ER)-positive tumors could have been treated with anti-hormonal therapy.

The *secondary objectives* of the pivotal study included: comparison between the two treatment groups on Progression-Free Survival (PFS); comparison between the two treatment groups of the Objective Tumor Response Rate (ORR) as measured using Response Evaluation Criteria in Solid Tumors (RECIST); Duration of Response (DoR); and assessment of standard safety parameters for oncology studies for all patients.

The *study was initiated* on 16 November 2006 (first patient), the *last date of enrollment* was 12 May 2009, and the data cut-off date was 12 May 2009. The final report was dated 19 March 2010. The two principal investigators were located at the Institute of Cancer Therapeutics, Bradford, UK, and the Weill Cornell Breast Center, New York, USA. The 135 study centres included 6 Australian sites.

The *study was conducted in accordance* with the requirements of the World Medical Association Declaration of Helsinki (Tokyo, 2004), the International Conference for Harmonization (ICH) guidelines on Good Clinical Practice (GCP) [CPMP/ICH/135/95], the European Clinical Trial Directive 2001/20/EC, and country specific requirements relating to clinical trials and drug regulation. The study was approved by site specific local and/or national Independent Ethics Committee (IEC)/Institutional Review Board (IRB). All patients provided written informed consent.

> **Comment:** The design of this study was open-label. Consequently, the study is subject to the well known biases associated with studies of this type. However, the study is considered to have been well conducted which mitigates, at least to some extent, the potential biases associated with the study design. Furthermore, the primary objective of the study was OS which is an objectively determined, unbiased endpoint.

7.1.1.1. Inclusion and exclusion criteria

Information on the inclusion and exclusion criteria are provided in the dossier. The study also included standard criteria for removing patients from therapy or assessment.

[3] Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, *et al.* Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377:914-23.

Comment: The inclusion and exclusion criteria are generally satisfactory for studies in women with heavily pre-treated locally recurrent or metastatic breast cancer. The inclusion criteria included prior treatment with at least 2 and not more than 5 chemotherapy regimens, and regimens had to include an anthracycline and a taxane (in any combination or order), unless contraindicated. The inclusion criteria did not require prior "failed" (refractory) treatment specifically with anthracyclines or taxanes. The inclusion criteria did not require prior treatment with capecitabine and/or vinorelbine. Both of these chemotherapy agents could be used in Australia consistently with their approved indications for third-line treatment of locally advanced or metastatic breast cancer previously treated with taxanes and anthracyclines.

7.1.1.2. Study treatments

7.1.1.2.1. Eribulin

Patients were pre-stratified based on geographic region, HER2/*neu* status, and prior treatment with capecitabine. Patients were randomised 2:1 to receive either eribulin as an iv bolus of 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 every 21 days or TPC. The protocol required eribulin dose reductions based on haematological and non-haematological toxicities. Eribulin was supplied by Eisai in vials containing 1 mg/2 mL eribulin as a 0.5 mg/mL solution in ethanol/water (5:95).

The following treatments were not permitted in the eribulin group: other investigational drugs; anti-tumor therapies such as chemotherapy and hormone therapy (irrespective of the reason for which it was being given); radiation therapy (other than required for palliation); gene therapy, biologics, or immunotherapy; due to the likelihood of drug interactions between eribulin and warfarin and related compounds, substitution of alternative agents for venous thromboembolic complications or requirement for anti-coagulation were mandated for patients randomised to eribulin. Mini-dose warfarin was permitted. While being discouraged, the concomitant use of unfractionated heparin and low molecular weight heparins appears to have been allowed, presumably based on individual patient considerations. If concomitant treatment continued with mini-dose warfarin or a related compound, then the PT/INR was to be closely monitored.

7.1.1.2.2. TPC

TPC was defined as any single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer, or best supportive care or radiotherapy, administered according to applicable local practice. Treatment with another investigational agent in the TPC group was not allowed. TPC was used from marketed supply and was provided by each site pharmacy. TPC administration and dose modification were done according to the package insert or local practice. The following concomitant treatments were not permitted in the TPC group: other investigational drugs; any other anti-tumor therapy that had not been identified as the TPC for a particular patient at the start of the study; and any drugs that were not allowed concomitantly with the selected TPC, according to the relevant package insert.

7.1.1.2.3. Treatment duration

Patients continued in the study until unacceptable toxicity, progression of disease, or until in the opinion of the investigator, discontinuation of therapy was in the best interest of the patient. Patients who demonstrated clinical benefit could continue treatment for as long as clinical benefit was sustained.

7.1.1.2.4. Allowed medications

Any medication considered necessary for the patient's welfare that was not expected to interfere with the evaluation of the study drug could be given at the discretion of the investigator. Ancillary treatments were to be given as medically indicated. All concomitant treatment or medication administered during the 30 days preceding first administration of the

investigational product, and throughout the study until 30 days after the final administration of the investigational product, were to be reported on the CRF.

Comment: The eribulin treatment regimen is considered to be reasonably based on prior Phase I/II dose escalation studies aimed at defining the MTD and DLTs. Eribulin dose modification based on haematological and non-haematological toxicities appears to be appropriate.

The sponsor stated that the TPC control was used as the comparator because "there is no clear standard of care after treatment with an anthracycline and a taxane for third-line or later treatment in patients with [metastatic breast cancer] MBC". The sponsor considered that the TPC comparator reflected current medical practice and "real-life choices in heavily pretreated MBC patients". Furthermore, the sponsor considered it "inappropriate to limit the treatment in the comparator arm to only those drugs available at the time of the protocol design" due to the rapidly changing availability of drugs used to treat breast cancer and the fact that the study was to last at least 18 months.

From an Australian perspective, it would have been preferable to have compared eribulin with capecitabine (rather than TPC), given that capecitabine is specifically approved in Australia for third-line treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline, and was approved for this indication at the time of the study. However, it is acknowledged that TPC is a pragmatic and appropriate clinical comparator in a large multi-national, multi-centre study in which treatment of the defined patient population is likely to differ among countries and centres.

The submission included a progress report on an ongoing Phase III study [301], with two co-primary endpoints (OS and PFS), comparing eribulin with capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes. The sponsor states (response to EMEA 120 day questions) that study 301 "is not directly relevant to the sought indication for this marketing application" as "it investigates the effectiveness of eribulin in a population with earlier stage disease (second-line therapy for advanced disease) than that included in Study 305 (where patients had more advanced disease)". However, the sponsor's statement regarding study 301 appears to be inconsistent with the outline of the study provided in the progress report which indicates that the study is comparing eribulin and capecitabine as third-line therapy for patients previously treated with anthracyclines and taxanes. This study is considered to be clinically important as will clarify the roles of eribulin and capecitabine for the treatment of the proposed patient population. The sponsor indicates that the results of this study should be available in 2013.

7.1.1.3. Efficacy variables and outcomes

7.1.1.3.1. Primary efficacy variable and endpoint

The *primary efficacy objective and endpoint* (pre-specified) was overall survival (OS), defined as the time from the date of randomisation until the date of death from any cause in the ITT population. Patient survival was recorded during the study. Following treatment discontinuation, survival information was collected every three months until death in all patients other than those who had withdrawn consent. Patients who were alive, had withdrawn consent or had been lost to follow-up were censored at the data cut-off date of 12 May 2009.

7.1.1.3.2. Secondary efficacy variables and endpoints

The *secondary efficacy objectives* were progression free survival (PFS), objective response rate (ORR), and duration of response (DoR).

PFS was defined as the time from randomisation until progressive disease or death due to any cause. PFS was censored for patients who did not have an event (i.e., those who were lost to follow-up or who had not progressed at the date of data cut-off). The *primary analysis of PFS*

was based on the *Independent review* of tumor assessment in the ITT population, with the date of objective disease progression being based on the date of radiological disease progression as assessed by the *Independent review* of imaging data using RECIST criteria. Patients without disease progression were censored on the date of their last radiological assessment preceding the start of any additional anti-cancer therapy. Patients were also censored if they discontinued randomised treatment and began any alternative anti-cancer therapy prior to progression in their disease. A *sensitivity analysis of PFS* was conducted based on the *Investigator's disease assessment*. In this investigator sensitivity analysis, the date of objective disease progression was defined as the earliest date of radiological disease progression based on imaging data using RECIST criteria or the date of symptomatic disease progression based on clinical assessment. For progressions based on the appearance of a new lesion, the date of progression was defined as the date of the assessment at which the new lesion was identified. For progressions based on an increase in the sum of LD, the date of progression was defined as the earliest assessment date on the target lesion page of the CRF showing this increase.

The *ORR was* defined as the confirmed number of patients with a complete response (CR) or partial response (PR) measured using RECIST criteria divided by the number of patients in the response evaluable. The *DoR* was defined as the time from first documented CR or PR until disease progression or death from any cause in the response evaluable population.

Comment: The primary efficacy endpoint of OS is appropriate as it represents an objectively determined clinical benefit of importance to patients with metastatic breast cancer. The censoring rules for the analysis of OS specified in the Protocol/Statistical Analysis Plan (SAP) were changed in the submitted analysis. In the Protocol/SAP, patients who were alive and those who were lost to follow up were to be censored at the date the patient was last known to be alive. However, in the final analysis of the OS, patients who were alive, withdrawn consent or had been lost to follow-up were censored at the data cut-off date of 12 May 2009.

The primary PFS analysis was based on the Independent review of tumour assessment using imaging (RECIST). The PFS analysis in the CSR and the associated progression/censoring rules were sated by the sponsor to have been developed after unblinding and differ from the analysis specified in the Protocol/SAP. Consequently, the PFS analysis in the CSR represents a *post-hoc* analysis. The new set of progression/censoring rules for the PSF are stated by the sponsor to have been formulated following discussion surrounding the interpretation of the FDA document "Guidance for Industry Clinical Trials for the Approval Cancer Drugs and Biologics". The main difference in the PFS analysis in the CSR from the one specified in the Protocol/SAP is that it takes into account progressions from non-target lesions (i.e., unequivocal progressions) in addition to new lesion and target lesion progression events. The details of the progression / censoring rules PFS (*post hoc*) analysis are provided in the in the CSR, as are those for the PFS (protocol specified) analysis.

The use of OS and PFS as the primary and secondary endpoints, respectively, is consistent with the relevant TGA adopted clinical guideline on the evaluation of anticancer medicinal products [CPMP/EWP/205/Rev.3/Corr.]. The guideline indicates that acceptable primary endpoints include OS and PFS/DS, and where PFS/DS is the selected primary endpoint OS should be report. The additional efficacy endpoints of ORR and DoR are considered to be acceptable. Tumour response was assessed by RECIST criteria, which are well accepted and commonly used criteria in clinical oncology studies investigating treatments, and undertaken by blinded Independent review which mitigates subjective assessment of disease progression by Investigators. The study did not include a quality of life endpoint, but this is considered acceptable in this study where the TPC included a variety of unblinded medications which might have introduced significant bias into quality of life assessments.

7.1.1.4. Assessments relevant to efficacy outcomes

Tumour baseline assessments (up to 28 days prior to start of study treatment) were performed with, at a minimum, CT or MRI scans with oral and iv contrast of the chest, abdomen, pelvis, and any other areas of suspected disease. Clinical lesions were only considered to be measurable when they were superficial (e.g. skin nodules and palpable lymph nodes). In the case of skin lesions, documentation was by photography, including a ruler to estimate the size of the lesion.

Tumour response was assessed by *Independent review* according to protocol specified Response Evaluation Criteria in Solid Tumours (RECIST) every 8 weeks (± 1 week), or sooner if there was suspicion of disease progression. The RECIST Criteria Quick Reference are provided in the Appendix to this evaluation report. Assessment was performed only in those areas where disease was found at Baseline, and any new areas of suspected disease. If possible, the same imaging modality and image acquisition protocol was to be used consistently across all assessment time-points. If tumor assessment was done by clinical exam (e.g. skin lesions), the protocol specified that assessment should, if possible, be made by the same investigator throughout the study. If subcutaneous masses or nodes were palpable and visible on CT/MRI scan, the protocol specified that tumor response assessment should be done using the CT/MRI scan, not clinical exam. If a superficial skin lesion was measurable (≥ 20 mm) and could not be evaluated by CT scan, then it was required to be documented by photography, incorporating a ruler with millimetre scale in the field of view.

Tumour response (complete [CR] and partial [PR]) required confirmation by a second examination performed no less than 4 weeks after the observed response. Patients with CR or PR or with stable disease (SD) who had been withdrawn from study treatment before disease progression, continued to have tumor assessments every 3 months until progressive disease (PD) or until start of a new anti-cancer treatment. Tumour response criteria were CR, PR, SD, PD, Not Evaluable (NE) and Unknown (UN) (information on relevant definitions was provided in the dossier).

Measurable disease criteria required the presence of at least one measurable lesion. If multiple measurable lesions were present, a maximum of 5 lesions per organ and 10 lesions in total, representative of all organs (i.e., representative of tumor burden) were to identified as *target lesions.* Target lesion were to be selected on the basis of size (longest diameter) and suitability for accurate repeated measurements. Target lesions should have excluded lesions for which radiotherapy was planned. Baseline measurement of *non-target* lesions was not required, but the presence or absence of these lesions should have been noted in the CRF during follow-up and the appearance of new lesions should have been recorded.

7.1.1.5. Randomisation and blinding methods

Patients were initially evaluated for eligibility by the investigator to ensure that the inclusion/exclusion criteria were satisfied. Furthermore, prior to randomisation the proposed TPC that would been given if the patient were randomised to TPC had to be defined and confirmed by the investigator using the interactive voice recognition system (IVRS). Once the TPC had been defined, patients were then randomised (2:1) to eribulin or TPC treatment according to the stratified randomisation schedule. Patients were stratified before randomisation based on geographic region (Region 1 [North America/Western Europe/Australia], Region 2 [Eastern Europe], and Region 3 [Latin America/South Africa], HER2/*neu* status (positive, negative or unknown), and prior treatment with capecitabine (yes or no).

This was an open label study and, consequently, neither patients nor investigators were blinded to treatment. However, the Eisai study team was blinded for OS data until the database lock to avoid potential bias. Independent statisticians conducted the interim analysis, and assisted with queries surrounding all death events. The Data Monitoring Committee (DMC) reviewed the interim data to determine whether the study should continue as planned, and the Eisai study

team did not have access to the interim data. The DMC was used to review the safety of eribulin treatment in the study, which ensured the sponsor remained blinded to the results until the primary analysis.

Imaging scans for tumor response using prespecified RECIST criteria were undertaken by centralized, blinded, independent review. Investigators were required to provide copies of all scans and images (preferably in digital format) to a central reading facility.

> **Comment:** The method of randomisation is considered to be acceptable. Stratification of patients on the basis of geographic region, HER2/*neu* status, and prior treatment with capecitabine is considered to be reasonable as these factors were potential confounders. Prior to randomisation, the particular TPC was required to be identified for each patient by the investigator using the IVRS. This allowed a subgroup analysis to be undertaken in which patients who were treated with eribulin, but who would have received the nominated TPC if they had been randomised to the TPC group, were compared with patients who had been randomised to the TPC group and received the nominated TPC.

7.1.1.6. Analysis populations

Intent-to-Treat (ITT) Population comprised all patients who were randomised, irrespective of whether or not they actually received the study treatment to which they had been randomised. The ITT population was the primary analysis population for all efficacy data.

Per Protocol (PP) Population comprised all patients in the ITT population who met the major inclusion Criteria 1 and 2 and who did not have any other major protocol violation. Major protocol violations included but were not limited to the following: patients who were treated on the opposite treatment group than the one to which they were randomised. The PP population was used for additional analyses of all efficacy endpoints.

Response Evaluable Population comprised all patients with measurable disease, defined as the presence of at least one measurable lesion based on RECIST criteria.

Exploratory subgroups included: *strata* (geographic region, HER2/*neu* status, and prior capecitabine treatment); *demographic characteristics* (age, group, race); receptor expression (ER Status, PR Status, hormonal receptor status [ER and PR], triple negative status [ER negative, PR negative and HER2/*neu* negative]); *disease characteristics* (visceral/non-visceral disease, number of organs involved); *prior chemotherapy* (number of prior chemotherapy regimens, number of prior chemotherapy regimens for advanced or metastatic disease, patients who progressed while on treatment with a taxane or other tubulin-inhibiting agent); and *TPC group* (hormonal therapy [all hormonal treatments]), chemotherapy (all chemotherapy treatments).

7.1.1.7. Sample size

The estimated sample size was calculated on the following assumptions: in addition to the final analysis based on OS there was to be one interim analysis; exponential distributions of overall survival; median overall survival of 9 months and 12 months in the TPC and eribulin groups, respectively (i.e. a hazard ratio of 0.75); 2:1 randomisation scheme; an overall 5% risk of erroneously claiming superiority of eribulin or TPC in the presence of no true underlying difference (two-sided Type I error); an 80% (power) probability of successfully detecting a difference if there is a 3 month increase in overall survival in subjects who receive eribulin over the 9 month survival in the TPC group; an average accrual rate of 35 patients per month and an accrual period of 18 months.

Based on the sample size assumptions, it was estimated that the study required 411 events (deaths). To achieve this number, initially an estimated total of 630 patients (420 in the eribulin group and 210 in TPC group) was planned to be enrolled, leading to an initial estimated maximum study duration of 26.5 months. As pre-specified in the protocol, the overall event rate in the pooled population was evaluated 15 months after the first patient was recruited. At the time of this re-assessment, the pooled sample suggested that the number of events was smaller

than expected. Consequently, the decision was made to increase the number of patients enrolled in order to achieve the required number of deaths sooner. Therefore, the initial sample size of 630 patients was increased to allow up to a maximum of 1000 patients. Sample size re-assessment was done on an ongoing basis in a blinded fashion. As soon as it became apparent that the 411 events (deaths) would be reached within a reasonable timeframe, recruitment was stopped.

7.1.1.8. Interim analysis

An interim analysis was performed when 50% of the deaths (206 deaths) had been observed. The study could have been stopped early for superiority or lack of OS efficacy. To maintain an overall significance level of 0.05, a Lan DeMets implementation of the O'Brien and Fleming alpha spending function was used to create a stopping rule for superior efficacy. With this approach, the nominal significance level of the interim test was 0.003 and the nominal level of the final analysis was 0.049. At the interim analysis, if the survival time in the eribulin arm was significantly better than the survival time in the TPC arm with a p-value of the stratified log-rank test of less than 0.003, then the study was to be stopped for superior efficacy. In addition, at the interim analysis, if the lower limit of the 95% CI for the hazard ratio (HR) for OS was higher than 0.85 then the study was to be terminated for lack of efficacy (i.e., futility). This hazard ratio was calculated from a Cox regression model containing treatment and the three stratification factors as covariates. Safety data were summarised and reviewed by the DMC at the time of the interim analysis.

> **Comment:** At the interim analysis, a significant treatment effect was detected using the cut-off criterion of an alpha of 0.003 (stratified log-rank test), and the p-value from the Cox model was p=0.0027 for the unadjusted analysis and p=0.0024 for the adjusted analysis. In the interim HR analysis the three stratification factors were analysed as covariates, but in the final HR analysis the factors were analysed as strata. The DMC noted that the stopping rule for superior efficacy had been crossed, but unanimously recommended that the study continue until the number of deaths outlined in the protocol had been achieved. The minutes from the relevant DMC meeting indicate that the factors taken into consideration by the committee were: the interests of the patients; the need to be able to draw valid scientific inferences from the data which stopping the study may jeopardize; the apparent evolving difference in treatment effect on survival between the 23 August 2008 data and the more recent data and therefore the robustness of the data; the comparative safety data; and examples from the literature where stopping boundaries have been crossed but trials have been continued.

7.1.1.9. Statistical methods

7.1.1.9.1. Overall survival (OS); the primary efficacy variable.

The study was designed to provide evidence to either support the null hypothesis that the survival distributions in the two treatment groups were equal [i.e. H0: $S_{E7389}(t)=S_{TPC}(t)$], or to reject the null hypothesis in favour of the alternative hypothesis that the survival distributions in the two treatment groups were not equal [i.e. H1: $S_{E7389}(t) \neq S_{TPC}(t)$].

In the primary analysis, OS was compared between eribulin and TPC in the ITT population using a two-sided stratified log-rank test at a significance level of 0.049 (i.e. adjusted for the interim analysis). The log-rank test was stratified by HER2/*neu* status, prior capecitabine treatment, and geographical region. The OS was summarised using Kaplan-Meier survival curves. The Kaplan-Meier estimate of median OS and first and third quartiles were presented with 95% CIs. The 1 and 2-year survival rates were provided with 95% CIs. The hazard ratio (with 95% CIs) was also provided based on a Cox regression model in which the three stratification factors were included as strata. Exploratory analyses of the OS in the pre-specified subgroups were also presented, as were post hoc subgroup exploratory analyses of the OS.

7.1.1.9.2. Progression free survival (PFS); a secondary efficacy objective.

The primary analysis of PFS was based on the Independent review of tumour assessment. PFS was summarised using Kaplan-Meier survival curves. The Kaplan-Meier estimate of the median PFS time and first and third quartiles were presented with 95% CIs. The 6 and 12 month PFS rates (with 95% CIs) were also presented. PFS was compared between the treatment groups using a two-sided stratified log-rank test at the 5% significance level. A sensitivity analysis of PFS was also conducted based on the Investigator's disease assessments. The PFS analyses were undertaken on both the ITT and PP populations.

7.1.1.9.3. Objective response rate (ORR); a secondary efficacy objective.

The ORR was defined as the number of patients with a confirmed CR or confirmed PR divided by the number of patients in the evaluable response population (primary analysis). The response rate was based on the *Independent review* of disease assessments. Subjects with unknown or missing responses were treated as non-responders, and were included in the denominator for calculating percentages. Exact Pearson-Clopper 2-sided 95% CIs the tumor response rates in each arm were calculated. A sensitivity analysis of ORR was conducted based on the *Investigator's disease assessments*. The evaluable response population was the primary analysis population, and the analysis was also undertaken on the ITT and PP populations.

7.1.1.9.4. Duration of response (DoR); a secondary efficacy objective.

The DoR was derived from the *Independent review* of best response. A sensitivity analysis was also conducted based on the *Investigator's disease assessments*. DoR was summarised using Kaplan-Meier survival curves. The Kaplan-Meier estimate of the median duration of response and first and third quartiles were be presented with 95% CIs. The evaluable response population was the primary analysis population, and the analysis was also undertaken on the ITT and PP populations.

> **Comment:** The statistical methods are considered to be satisfactory, and standard for analyzing studies of this type. However, the study included three secondary objectives and no adjustment of the significance level was made for the three pairwise comparisons to account for multiplicity. The study design required no imputation for missing survival data.

7.1.1.10. Participant flow

A total of 762 patients were randomised and included in the ITT population; 508 to the eribulin group and 254 to the TPC group. Discontinuation before the start of treatment occurred in 12 patients (6 in each treatment group), and 1 patient initially randomised to the TPC group was mistakenly re-randomised to the eribulin group. Progressive disease assessed according to RECIST criteria was the main reason for premature discontinuation in both treatment groups (66.1% and 60.2% of randomised patients in the eribulin group and the TPC group, respectively). The survival status was known for most patients in both treatment groups at the data cut-off point (i.e. 99.2% of randomised patients in both treatment groups). Patient disposition in the original data is summarised below in Table 18 (an updated annotated flow chart was also provided).

Table 18: Study 305 – Patient disposition.

	Treatment Group		Total
	Eribulin N = 508 n (%)[a]	TPC N = 254 n (%)[a]	N = 762 n (%)[a]
Randomized	508	254	762
Intent-to-Treat Population[b]	508 (100.0)	254 (100.0)	762 (100.0)
Safety Population[c]	503 (99.0)	247 (97.2)	750 (98.4)
Response Evaluable Population[d]	468 (92.1)	214 (84.3)	682 (89.5)
Per Protocol Population[e]	459 (90.4)	216 (85.0)	675 (88.6)
Discontinued from study treatment	484 (95.3)	244 (96.1)	728 (95.5)
Reason for discontinuation from study treatment[f]:			
Adverse Events (including toxicity)	50 (9.8)	24 (9.4)	74 (9.7)
Withdrew Consent	10 (2.0)	7 (2.8)	17 (2.2)
Progressive Disease according to RECIST criteria	336 (66.1)	153 (60.2)	489 (64.2)
Clinical progression	61 (12.0)	36 (14.2)	97 (12.7)
Physician's decision	18 (3.5)	13 (5.1)	31 (4.1)
Lost to Follow-up	0 (0)	0 (0)	0 (0)
Death	3 (0.6)	2 (0.8)	5 (0.7)
Other	6 (1.2)	9 (3.5)	15 (2.0)
Survival Status at data cut-off			
Alive	230 (45.3)	104 (40.9)	334 (43.8)
Died	274 (53.9)	148 (58.3)	422 (55.4)
Lost to Follow-up	4 (0.8)	2 (0.8)	6 (0.8)

(a) Percentages are based on all randomised patients.
(b) Intent-to-Treat Population - All patients who were randomised irrespective of whether or not they actually received medication.
(c) Safety Population - All patients who were randomised and who received at least a partial dose of study treatment.
(d) Response Evaluable Population - All patients with measurable disease, defined as the presence of at least one measurable lesion, per Response Evaluation Criteria in Solid Tumors by Independent Review.
(e) Per Protocol Population - All patients in the Intent-to-Treat Population who had met the major inclusion Criteria 1 and 2 and who did not have any other specified major protocol violation.
(f) Reasons for discontinuation are based on the planned treatment in the ITT Population.

The most common therapy type in the TPC group was chemotherapy, which was planned for 246 (96.9%) patients and received by 238 (93.7%) patients in the ITT population. The five most common chemotherapies planned in patients in the TPC group were vinorelbine (65, 25.6%), gemcitabine (46, 18.1%), capecitabine (45, 17.7%), taxanes (41, 16.1%), and anthracyclines (24, 9.4%). The five most common chemotherapies actually received by patients randomised to the TPC group (ITT population) were vinorelbine (61 , 24.0%), gemcitabine (46, 18.1%), capecitabine (44, 17.3%), taxanes (38, 15.0%), and anthracyclines (24, 9.4%). Only 2 hormonal treatments were received by more than 1 patient: fulvestrant (4, 1.6%) and letrozole (3, 1.2%,). There were 2 patients who received more than 1 TPC: 1 received gemcitabine and paclitaxel in combination; and 1 received cyclophosphamide and methotrexate in combination.

> **Comment:** The majority of patients in the TPC group were treated with chemotherapy (93.7%) with the remainder being treated with hormonal therapy. Although best supportive care was one of the TPC treatment options, no patients were managed with this option. The 5 most common TPC treatments included both vinorelbine (the most common) and capecitabine (the third most common). The evaluator is unaware of Australian data on the comparative use of treatments for third-line treatment of locally advanced or metastatic breast cancer in patients previously treated with anthracyclines and taxanes.

7.1.1.11. Major protocol violations/deviations

There were 77 (10.1%) patients with protocol deviations from inclusion/exclusion criteria (44 [8.7%] in the eribulin group and 33 [13.0%] in the TPC group). The most frequently observed deviations from the inclusion/exclusion criteria (eribulin vs TPC) related to patients not being refractory to the most recent chemotherapy (16 [3.1%] vs 11 [4.3%]), followed by patients receiving more than five prior chemotherapy regimens (15 [3.0%] vs 9 [3.5%]), and patients receiving only one regimen for locally recurrent or metastatic disease (7 [1.4%] vs 8 [3.1%]). The 77 patients with protocol deviations from the inclusion/exclusion criteria were excluded from the PP population, and an additional 10 patients were excluded because they did not receive study treatment.

> **Comment:** There was a significant proportion (10.1%) of patients with protocol deviations relating to compliance with the inclusion/exclusion criteria, and an imbalance in total deviations between the eribulin (8.7%) and the TPC (13.0%) groups. However, the most frequently reported deviations were reasonably evenly distributed between the two treatment groups. Consequently, it is considered that the protocol violations are unlikely to have significantly biased the study. However, the frequency of the total violations raises some concerns about the adequacy of the monitoring used to ensure compliance with the inclusion/exclusion criteria prior to randomisation.

7.1.1.12. Baseline data

7.1.1.12.1. Demographics

The mean (SD) age of the ITT population (n=762) was 55.2 (10.4) years [range:27,85], and the majority were "White" (34, 4.5%). The age distribution was 51 (6.7%) < 40 years, 560 (73.5%) ≥ 40 to < 65 years, and 151 (19.8%) ≥ 65 years. Most patients were post-menopausal (578 [75.9%]). Most patients (488 [64.0%]) were from North America/Western Europe/Australia.

Comment: The basic demographic data were well balanced between the two treatment groups and are considered to be generally representative of the Australian female population who might be candidates for the treatment with eribulin. However, the mean age of the total patient population was 55.2 years and the mean time since original diagnosis was 6.7 years which suggests that mean age at first diagnosis was about 48 to 49 years. This is notably younger than the mean age of first diagnosis of breast cancer in women in Australia of 60.3 years.[4]

7.1.1.12.2. Breast cancer disease characteristics

The mean (SD) duration of disease (time from first diagnosis of breast cancer to first dose of eribulin or TPC) was 6.7 (5.0) years. The most common tumor site at baseline was bone, which was reported in 464 (60.9%) patients. Most patients had 1, 2, or 3 disease involved organs at baseline (120 [15.7%], 254 [33.3%], and 222 [29.1%], respectively). The most frequently reported cancer stage at diagnosis in patients in both groups was Stage II (213 [41.9%] and 89 [35.0%], eribulin and TPC, respectively). There was a lower proportion of patients in the eribulin group with Stage IV disease at diagnosis compared with the TPC group (81 [15.9%] and 59 [23.2%], respectively). Cancer staging at diagnosis by major stage is summarised in Table 19.

[4] Australian Institute of Health and Welfare & Australian Association of Cancer Registries 2010. Cancer in Australia: an overview 2010. Cancer series no. 60. Cat. no. Can 46. Canberra. AIHW.

Table 19: Study 305 - Cancer staging at diagnosis updated to report data by major stage; ITT population.

Parameter	Treatment Group		Total
	Eribulin N=508 n (%)	TPC N=254 n (%)	N=762 n (%)
Cancer staging at diagnosis			
0	2 (0.4)	0	2 (0.3)
I	62 (12.2)	30 (11.8)	92 (12.1)
II	213 (41.9)	89 (35.0)	302 (39.6)
III	142 (28.0)	71 (28.0)	213 (28.0)
IV	81 (15.9)	59 (23.2)	140 (18.4)
Not available	8 (1.6)	5 (2.0)	13 (1.7)

Overall, 42.0% of patients were ECOG Performance Status 0 (i.e., fully active), 48.6% were Status 1 (i.e., restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature) and 8.0% were Status 2 (i.e. ambulatory and capable of all self care but unable to carry out any work activities, up and about more than 50% of waking hours). Where hormonal receptor status was known, 507 (70.1%) patients were ER+, and 377 (55.7%) were PgR+. Where HER2/neu status was known, 265 (81.6%) patients were positive and 123 (17.8%) were negative.

> **Comment:** Baseline breast cancer disease characteristics were generally evenly distributed between the two treatment groups, although there were some minor imbalances between the two groups in cancer staging at diagnosis. The summary of cancer staging at diagnosis in the ITT population included 2 patients in the eribulin group who were classified as stage 0. The AJCC breast cancer staging criteria define stage 0 as *in situ* cancer that has not spread to lymph nodes or distant sites. Consequently, these 2 patients should not have been included in the study. Presumably, these 2 patients are those identified in Listing 16.2.4.4 (Histological/Cytological Diagnosis, All Randomised Patients) as ID 14011001 (ductal adenocarcinoma, Cancer Staging 0, TNM Classification 0/0/0), and ID 14011008 (ductal adenocarcinoma, Cancer Staging 0, TNM Classification 0/0/0).

7.1.1.12.3. Disease characteristics other than breast cancer

Overall, 692 (90.8%) patients were reported as having significant medical history (any) other than breast cancer (464 [91.3%] and 228 [89.8%], eribulin and TPC, respectively). Significant medical conditions were most frequently reported in the cardiovascular system (294 [38.6%] patients). The musculoskeletal system, renal/genitourinary system and gastrointestinal systems all had >30% of patients with significant medical history (271 [35.6%], 249 [32.7%] and 239 [31.4%] respectively). On no occasion was there a > 5% difference between the two treatment groups for significant medical conditions (any body system).

Overall, 644 (84.5%) patients were reported with baseline signs or symptoms. Baseline signs and symptoms were most frequently reported in the musculoskeletal and connective tissue category (314 [41.2%] patients), followed by general disorders and administration site conditions (251 [32.9%] patients) and nervous system disorders (201 [26.4%] patients). Hepatobiliary disorder symptoms and signs were reported in 10 (2.0%) patients in the eribulin group and 8 (3.1%) patients in the TPC group. Liver metastases were also common at baseline (296 [58.3%] patients in the eribulin group and 159 [62.6%] patients in the TPC group).

> **Comment:** Baseline disease characteristics other than breast cancer were similarly distributed in the two treatment groups. Examination of the significant medical / surgical history tabulated summary in the ITT population showed no significant imbalances between the two treatment groups.

7.1.1.12.4. Prior and concomitant medication and other product use

Most patients in the ITT population had received several prior chemotherapies, with the median duration of the last chemotherapy being 3.53 months [range: 0, 32.0 months]. A total of 754 (99.0%) patients had previously been treated with a taxane, 752 (98.7%) with an anthracycline, and 559 (73.4%) with capecitabine. Anthracyclines and taxanes had been used as either adjuvant therapy or as treatment for locally recurrent or metastatic disease. Of the 8 patients who had not previously received a taxane, 3 had a contraindication, and of the 10 patients who had not previously received an anthracycline, 5 had a contraindication. Most patients (614 [80.6%]) were reported as refractory to a taxane, with the corresponding figures for capecitabine being 516 (67.7%), and 444 (57.7%) for anthracyclines. In this study "refractory" was defined as progressed within 6 months of receiving therapy. Most patients had received prior treatment with radiotherapy (615 [80.7%]). Information on prior treatments for cancer was included in the dossier.

Overall, 572 patients (76.3%) in the safety population received other medications within 30 days prior to start of study treatment (383 [76.1%] and 189 [76.5%], eribulin and TPC, respectively). The most frequently used prior medication in patients in both treatment groups was zoledronic acid (69 [13.7%] and 34 [13.8%], eribulin and TPC, respectively). Paracetamol was used by 48 (9.5%) patients in the eribulin group and 32 (13.0%) patients in the TPC group. All other medications were used by <10% of patients in either treatment group.

The most frequently used concomitant medication by patients in both treatment groups (safety population) was dexamethasone (192 [38.2%] and 84 [34.0%], eribulin and TPC, respectively). The use of paracetamol, granulocyte colony stimulating factor, ondansetron, ciprofloxacin and granisetron was ≥ 5% higher in the eribulin group than in the TPC group, and the use of ranitidine was ≥ 5% higher in the TPC group than in the eribulin group.

> **Comment:** There were imbalances between the two treatment groups in the prior use of medicines other than anti-cancer treatments and in the use of concomitant medicines. However, these imbalances are considered not to have biased the results of the study.
>
> It is noted that the concomitant use of granulocyte stimulating factor was 10% higher in the eribulin group (89 [17.7%] patients) than in the TPC group (89 [7.7%] patients), and the concomitant use of ciprofloxacin was ~10% higher in the eribulin group (72 [14.3%] patients) than in the TPC group (12 [14.9%]). These differences are likely to reflect the increased risk of neutropenia, febrile neutropenia, and infections in patients in the eribulin group compared with the TPC group.

7.1.2. Results for the primary efficacy outcome (OS)

7.1.2.1. Original OS data

The key results for the primary analysis of OS in the ITT population are summarised below in Table 20 (the CSR also included summaries for additional analyses of the OS), and the Kaplan-Meier curves for OS are provided in below in Figure 6.

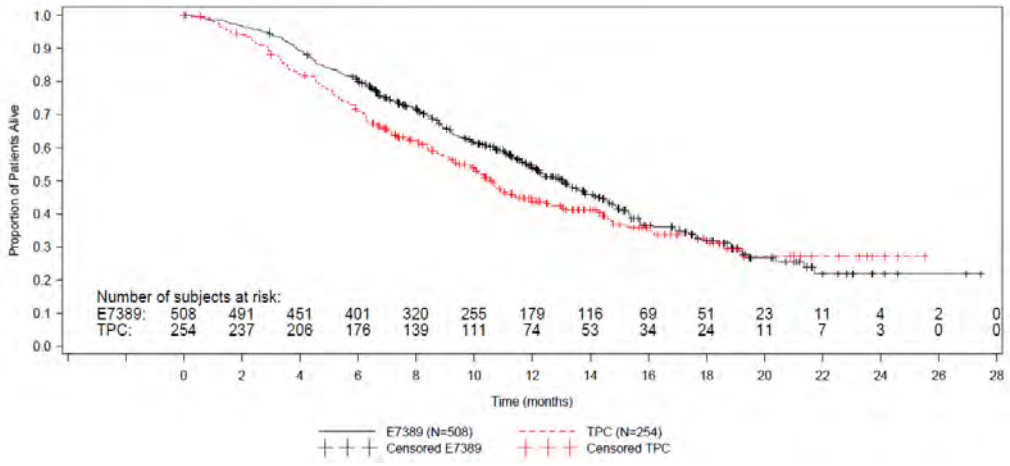
Table 20: Study 305 – Overall survival (OS) analysis in the original data; ITT population.

	Eribulin (n=508)	TPC (n=254)
Number of patients who died – n (%)	274 (53.9%)	148 (58.3%)
Number of patients censored – n (%)	234 (46.1%)	106 (41.7%)
Overall survival – median, days [95% CI]	**399 [95% CI: 360, 434]**	**324 [95% CI: 282, 380]**

	Eribulin (n=508)	TPC (n=254)
Difference in median OS – days [95%CI]	**75.0 [95% CI: 21.4, 128.6]**	
Stratified log-rank test	**p = 0.041**	
HR [eribulin/TBC] [a]	**0.809 [95% CI: 0.660, 0.991]**	

a: HR based on a Cox model including HER2/*neu* status, prior capecitabine treatment, and geographical region as strata.

Figure 6: Study 305 – Kaplan-Meier curves of overall survival (OS) in the original data; ITT population.



Comment: The OS data were censored for patients who were still alive at the date of data cut-off (12 May 2009) or who were lost to follow-up before the date of data cut-off. Only 6 patients (4 in the eribulin group and 2 patients in the TPC group) were lost to follow-up at the data cut-off. Therefore, the survival status of the majority of patients was confirmed at the date of data cut-off. The primary analysis of the original data took place when a total of 422 deaths had been recorded (i.e., 55.4% of enrolled patients). The results of the primary analysis of the OS in the ITT population showed that median survival in the eribulin group was statistically significantly longer than in the TPC. The difference in the medians of 75.0 days [95% CI: 21.4, 128.6] is small, but is considered to be clinically meaningful in women with heavily pretreated advanced metastatic breast cancer. However, the p value for the stratified log-rank test was 0.041, which is not particularly robust as the significance level for the study was set at p=0.049 (adjusted due to the interim analysis). The HR (based on a Cox model including HER2/neu status, prior capecitabine treatment, and geographical region as strata) showed that the risk of death over the duration of the study was about 20% lower for patients in the eribulin group compared with the TPC group, and that this was statistically significant [95% CI: 0.9%, 34%].

The Kaplan-Meier survival curves showed that the difference between the two treatments began to emerge at about 2 months after initiation of treatment. However, the curves are noted to cross-over at about 18 to 20 months. In general, cross-over of Kaplan-Meier survival curves raises concerns about the interpretation of the HR as it may indicate that the hazard functions are not proportional (i.e., proportionality requires the curves to be parallel, subject to random variation). However, in the current case crossing over occurred towards the end of the curves when the number of patients in the two groups alive and uncensored were getting small, which increases the variability in the survival estimates. Consequently, it is likely that small patient numbers are the reason for the cross-over rather than violation of proportionality of the hazard functions.

The 1-year survival rate in the ITT population was greater in the eribulin group than in the TPC group (53.9% [95% CI: 49.2, 58.6] and 43.7% [95% CI: 37.1, 50.2], respectively), while the reverse was seen for the 2-year survival rate (21.9% [95% CI: 14.8, 29.0] and 27.2% [95% CI: 18.8, 35.5], respectively). However, by 2 years only 7 patients were alive and uncensored (4 in the eribulin group and 3 in the TPC group) making interpretation of the data at this time point not meaningful.

The analysis of OS in the PP population showed that although the HR was similar to that for the analysis in the ITT population (0.812 and 0.809), the stratified log-rank test in the PP population was not statistically significant (p=0.066 [c.f., p=0.041 in the ITT population]). The failure of the HR to demonstrate statistical significance in the PP population suggests that the sample size was too small to provide the analysis with adequate power.

7.1.2.2. Updated OS data

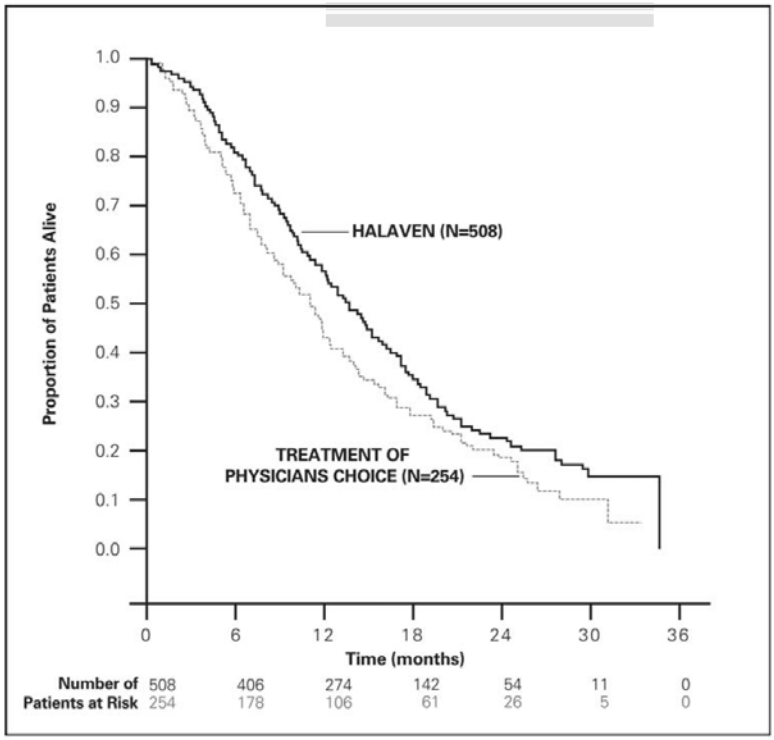
In response to 120 day questions from the EMEA the sponsor provided an updated OS analysis from study 305 "based on more mature [OS] data" at the data cut-off date of 3 March 2010. This updated OS analysis was not specified in the study protocol. The updated report analyzed OS data evaluated at 589 events (77.3% of enrolled patients) compared with 422 events (55.4% of enrolled patients) for the original report. The key results of the updated OS analysis are summarised below in Table 21, and the Kaplan-Meier curves for the updated OS analysis are provided below in Figure 7.

Table 21: Study 305 – Overall survival (OS) analysis in the updated data; ITT population.

	Eribulin (n=508)	TPC (n=254)
Number of patients who died – n (%)	386 (76.0%)	203 (79.9%)
Number of patients alive – n (%)	113 (22.2%)	46 (18.1%)
Lost to follow-up or withdrew consent	9 (1.8%)	5 (2.0%)
Overall survival – median , days [95% CI]	**403 [95% CI: 367, 438]**	**321 [95% CI: 281, 365]**
Difference in median OS – days [95%CI]	**82 [95% CI: 29.9, 134.1]**	
Stratified log-rank test	**0.014**	
HR [eribulin/TBC] [a]	**0.805 [95% CI: 0.667, 0.958]**	

a: HR based on a Cox model including HER2/neu status, prior capecitabine treatment, and geographical region as strata.

Figure 7: Study 305 – Kaplan-Meier curves of updated overall survival (OS); ITT population.



Source: Study 305, Sponsor's 120 day response to EMEA.

Comment: The results of the updated OS analysis were consistent with those from the original OS analysis. The Kaplan-Meier curves of OS in the updated data (ITT population) no longer cross-over confirming that the cross-over in the original data was most likely due to small patient numbers at the cross-over point. In addition, in contrast to the original the updated analysis of OS in the PP population was statistically significant for the comparison between the two treatment groups: HR = 0.778 [95% CI: 0.645, 0.939]; p=0.009.

7.1.3. Results for the secondary efficacy outcomes

7.1.3.1. Progression Free Survival (PFS)

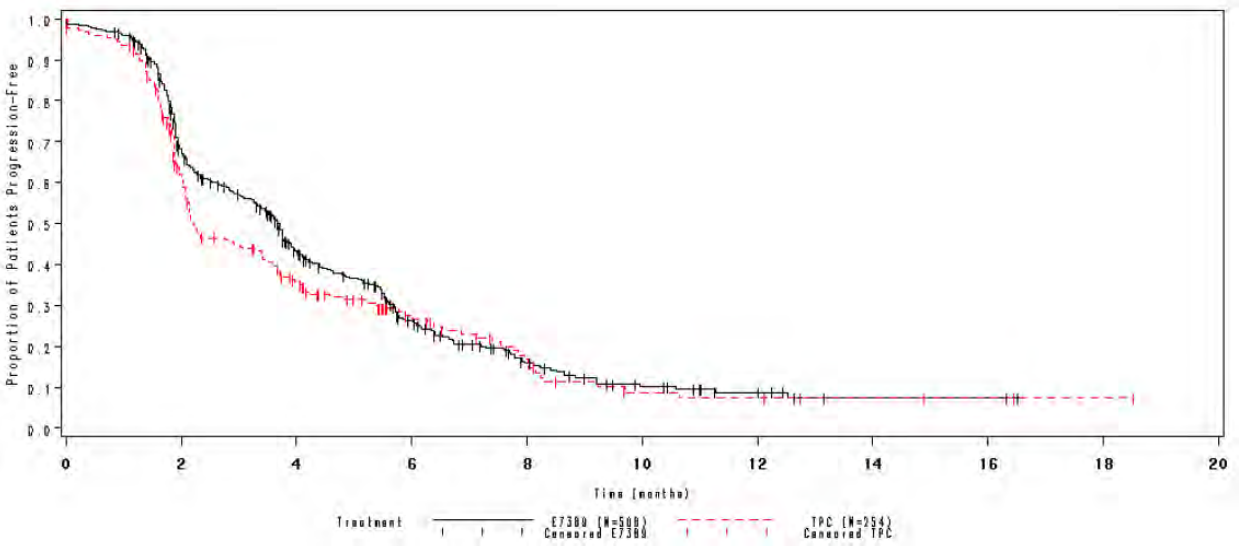
The results for primary analysis of PFS by the *Independent review* are summarised in Table 22. The PFS results based on the *Independent review* (primary analysis) and the *Investigator review* (sensitivity analysis) are provided in the submission and the Kaplan-Meier curves for the primary analysis (*Independent review*) of the PFS are provided in Figure 8.

Table 22: Study 305 – Summary of the primary analysis of PFS by the Independent review; ITT population.

	Eribulin (n=508)	TPC (n=254)
Number of events – n (%)	357 (70.3%)	164 (64.6%)
PFS – median, days [95% CI]	113 [95% CI: 101, 118]	68 [95% CI: 63, 103]
Stratified log-rank test	p=0.137	
HR [eribulin/TBC] [a]	0.865 [95% CI: 0.714, 1.048]	

a: HR based on a Cox model including HER2/*neu* status, prior capecitabine treatment, and geographical region as strata.

Figure 8: Study 305 – Kaplan-Meier analysis of PFS by the Independent review; ITT population.



Comment: In both the Independent review (primary analysis) and the Investigator review (sensitivity analysis), median PFS was longer in the eribulin group than in the TPC group, but the difference was statistically significant only for the Investigator review. However, the median PFS was similar in both the Independent and Investigator reviews for both the eribulin and TPC groups. The median difference between the between the two treatment groups was in favour of eribulin in both the Independent review (45 days) and the Investigator review (44 days). Overall, it is considered that the PFS results for the Independent and Investigator reviews are clinically similar.

The difference in statistical significance in the ITT population between the two reviews appears to result from the lower proportion of patients censored in the *Investigator review* compared with the *Independent review* due to the different methods adopted to determine disease progression. The sponsor states that this difference "is because the Independent blind review is associated with some limitations". The sponsor comments that patients were no longer scanned when the Investigator deemed that they had PD based on RECIST. Consequently, these patients were censored in the Independent review (irrespective of whether the Independent reviewer disagreed or agreed with the Investigator) and no further scans were undertaken on these patients. In addition, progression of patients with non-measureable disease could only be assessed by Independent review if non-target lesions progressed or if new lesions appeared. Finally,

patients who progressed clinically without radiologic findings could not be assessed by Independent review. Despite the limitations raised by the sponsor, it is considered that the blinded *Independent review* of PFS based on objective imaging data using RECIST criteria is less subject to bias than the *Investigator review,* particularly in a study in which neither the investigators nor patients were blinded to treatment.

7.1.3.2. Objective Response Rate (ORR)

The ORR was defined as the number of patients with a confirmed CR or confirmed PR divided by the number of patients in the evaluable response population. In the *Independent review* (primary analysis), the ORR was 12.2% [95% CI: 9.4, 15.5] for patients in the eribulin group (57/468) and 4.7% [95% CI: 2.3, 8.4) for patients in the TPC group (10/214); p=0.002, Fisher's exact test. The major contributor to the ORR in both treatment groups was the PR (11.5% [n=54] and 4.7% [n=10], eribulin and TPC, respectively), with the CR being 0.6% [n=3] in the eribulin group and 0% [n=0] in the TPC group. The ORR based on the *Investigator review* (sensitivity analysis) was consistent with the *Independent review* (primary analysis).

Comment: In both the Independent review (primary analysis) and the Investigator review (sensitivity analysis), the ORR was statistically significantly higher in the eribulin group than in the TPC group.

7.1.3.3. Duration of Response (DoR)

The DoR was defined as the time from the first documented evidence of CR or PR until the first documented sign of disease progression or death due to any cause. In the *Independent review* (primary analysis), the median duration of response was 128 days [95% CI: 116, 152] in the eribulin group (progressed [n=31], censored [n=26]), and 205 days [95% CI: 205, 212]) in the TPC group (progressed [n=3], censored [n=7]); p=0.159, log-rank test.

Comment: The duration of response was non-statistically significantly longer in the TPC group compared with the eribulin group. However, it is considered that the number of patients in the TPC group included in the analysis is too small to provide a meaningful comparison between the two treatment groups.

7.1.4. Subgroup analyses of OS

7.1.4.1. Pre-specified subgroup analyses

The study included a number of pre-specified subgroup analyses of OS. However, the study was not designed to assess the statistical significance of the subgroup comparisons between the two treatment groups on OS. No statistical adjustment was made for the multiple comparisons which increases the risk of statistically significant results being observed by chance. Consequently, all subgroup analyses should be considered to be exploratory. The trend in nearly all the subgroup analyses was for OS to favour patients in the eribulin group compared with the patients in the TPC group.

The subgroup analyses of OS in which the between treatment comparisons statistically favoured the eribulin group over the TPC group were: patients in the North America / Western Europe /Australian geographical group (HR = 0.724 [95% CI: 0.658, 0.924]); patients previously treated with capecitabine (HR = 0.771 [95% CI: 0.612, 0.973]); hormonal receptor negative patients (HR = 0.663 [95% CI: 0.445, 0.987]); previous chemotherapy received as TPC (HR = 0.907 [95% CI: 0.656, 0.993]); patients with visceral disease (HR = 0.771 [95% CI: 0,620, 0.960]); patients aged ≥ 40 years to < 65 years (HR = 0.760 [95% CI: 0.599, 0.964]); and patients with racial classification white (HR = 0.788 [95% CI: 0.636, 0.975]).

Comment: In the 120 day questions, the EMEA raised an issue relating to the difference in OS between eribulin and TPC for the subgroup analyses involving patients previously treated with capecitabine (pre-treated) and patients not previously treated with capecitabine (capecitabine naïve). In pre-treated capecitabine patients, the HR

statistically significantly favoured eribulin compared with TPC: HR = 0.771 [95% CI: 0.612, 0.973]; p=0.028, log-rank test. However, in capecitabine-naïve patients, while the HR favoured eribulin compared with TPC the result was not statistically significant: HR = 0.993 [95% CI: 0.617, 1.443]; p=0.787, log-rank test. The EMEA commented that the "apparently reduced benefit of eribulin vs. TPC in capecitabine naïve patients: HR 0.94, compared with 0.77 in patients previously treated with capecitabine is a cause for concern". The EMEA requested the sponsor to "justify the indication in capecitabine naïve patients".

In the response, the sponsor notes that the majority of patients enrolled in the study had been previously pre-treated with capecitabine (73% [559/762]) as opposed to those who were capecitabine naïve (27% [203/762]). The sponsor states that "[A]lthough not powered to detect a significant difference by subgroup, data showed a benefit for eribulin in both capecitabine pre-treated and naïve subgroups. Thus, Eisai does not consider it necessary to exclude capecitabine-naïve patients from treatment with eribulin". The sponsor noted that "given that there is substantial overlap in the estimates of the ...HRs [for the two subgroup comparisons]... and those CIs encompass the estimates of the hazard ratios of the two subgroups, the statistical analysis does not support a difference between the two subgroups and the CIs are wide enough that a substantial benefit is very possible".

The arguments supporting the efficacy of eribulin in capecitabine-naïve patients based on the width of the 95% CIs for the OS are considered to unacceptable. Wide 95% CIs suggest high intersubject variability and/or an underpowered study. Furthermore, it is considered that is erroneous to state that the wide 95% CI for OS could possibly support a substantial benefit toward eribulin treatment in capecitabine-naïve patients when it could be stated with equal validity that the wide 95% CI for OS could possibly support a substantial benefit toward TPC treatment. In addition, no evidentiary weight can be given to the observation that such a broad 95% CI for OS in capecitabine naïve patients encompasses the point estimate for the OS in capecitabine treated patients.

The sponsor also provided post-hoc analyses of PFS (Investigator review, original date) and ORR (Independent review, original data) according to prior capecitabine treatment. The sponsor claimed that the results for these two post-hoc analyses were consistent with the results for the OS analysis. For PFS, the HR statistically favoured eribulin over TPC in capecitabine pre-treated patients (HR=0.679 [95% CI: 0.557, 0.828), but in capecitabine naïve patients there was no statistically significant difference between the two treatment groups (HR = 1.030 [95% CI: 0.731, 1.435]. The sponsor commented that difference in effect in the capecitabine pre-treated and naïve analyses "appears to be driven by results in the TPC group. The median PFS was 110 days and 108 days with eribulin in the capecitabine-pretreated and capecitabine-naïve patients respectively, showing a similar effect of eribulin whether patients had previously received capecitabine or not. In contrast, in the TPC arm, median PFS was 63 days and 114 days in the capecitabine-pretreated and capecitabine-naïve patients, respectively, which was mainly driven by capecitabine-naïve patients receiving capecitabine". In the ORR analysis, ORR was 11.6% [95% CI: 8.4, 15.4] with eribulin and 4.5% [95% CI 1.8, 9.0) with TPC in capecitabine pre-treated patients, and 13.9% [95% CI 8.3, 21.4] with eribulin and 5.2% (95% CI: 1.1, 14.4) with TPC in capecitabine naïve patients. There was no statistical analysis of the ORR results.

The sponsor concluded that "the PFS and ORR results support that eribulin is effective in the treatment of capecitabine-pretreated and capecitabine-naïve patients, and are consistent with the original OS analysis results. Given that the data show a survival benefit for eribulin in both sub-groups, Eisai believes it is appropriate to provide capecitabine-naïve patients an option to receive eribulin in this late-line setting".

Irrespective of the sponsor's arguments justifying eribulin treatment in capecitabine naïve patients, it is considered that it would be difficult to defend denying treatment with eribulin to capecitabine-naïve patients based on the data from an underpowered, subgroup analysis.

7.1.4.2. Post-hoc subgroup analyses

7.1.4.2.1. Treatment comparison of OS by chemotherapy refractoriness

The Summary of Clinical Efficacy [Module 2.7.3] included a *post-hoc* subgroup analysis of OS (HR [95% CI]) by chemotherapy refractoriness (defined as disease progression within 60 days of taking the last dose). This analysis showed that OS was statistically significantly longer in the eribulin group compared with the TPC group in patients who were not refractory to anthracycline or taxane, and were refractory to capecitabine or vinorelbine. The analysis also showed that there was no statistically significant difference in OS between the two treatment groups in anthracycline refractory patients, taxane refractory patients, capecitabine non-refractory patients, vinorelbine non-refractory patients and gemcitabine patients (refractory and non-refractory). In addition, there was no statistically significant difference in OS between the two treatment groups in the combined group anthracycline/taxane/capecitabine patients who were refractory or non-refractory.

> **Comment:** In the post-hoc subgroup analysis of chemotherapy refractoriness, refractory to medication was defined as disease progression within 60 days of taking last dose. This definition differed from that in the inclusion criteria in which refractory to medication was defined as progression on or within 6 months of therapy. The EMEA questioned the reasons for this difference, and the sponsor responded by stating that the 60 day interval was chosen for the post hoc subgroup analysis "since this is the generally accepted average time frame used in clinical practice to follow-up...patients with imaging scans, after stopping ...chemotherapy". The sponsor also provided Forest plots of the OS results using the 60 day definition and the 6 month definition. These plots showed no significant difference between the refractory data derived from the 6 month and 60 day definitions.
>
> In the 120 day questions, the EMEA also commented that the benefit of eribulin compared with the TPC on OS appeared to be limited in taxane refractory patients (HR = 0.98 [95% CI: 0.74, 1.30]), compared with patients not taxane refractory (HR = 0.63 [95% CI: 0,46, 0.87]). The EMEA requested the sponsor to justify the indication in taxane refractory patients. The sponsor provided updated data for OS by chemotherapy refractoriness (60 day definition) which were generally consistent with the original data (60 day definition). The updated data showed a statistically significant OS benefit for eribulin compared with TPC in patients not taxane refractory (HR = 0.73 [95% CI 0.56, 0.96]), while the OS benefit for eribulin compared with TPC in taxane refractory patients was not statistically significant (HR = 0.90 [95% CI 0.71, 1.14]). The sponsor commented that the HRs for the two subgroups (taxane refractory, not taxane refractory) are closer in the OS update, with an overlap of the HR point estimates for both subgroups with the 95% CI for the other subgroup. In addition, the HR in taxane refractory patients also showed an improved benefit with eribulin compared with TPC in the OS update compared with the original analysis.
>
> The sponsor concluded that "although not powered to detect a significant difference by subgroup, the OS update data showed a benefit for eribulin in patients who were taxane-refractory as well as those who were not taxane-refractory. Thus, Eisai does not consider it necessary to exclude taxane-refractory patients from treatment with eribulin". The sponsor also commented that in clinical practice it is known that patients who are refractory to paclitaxel "still have a chance or responding to docetaxel, or other tubulin-affecting drugs". Consequently, the sponsor argued that rechallenging taxane refractory patients with another "tubulin-affecting drug like eribulin" could be justified, particularly

given the results for the updated OS analysis which showed a benefit for eribulin compared with TPC in taxane refractory patients.

The sponsor also provided PFS results from the Investigator review of the original data in taxane refractory and not taxane refractory patients. These results showed that there was a statistically significant OS benefit for patients in the eribulin group compared with TPC in both taxane refractory and not taxane refractory patients (60, days definition of refractory). The ORR data provided by the sponsor also showed that the response in eribulin treated patients in the taxane refractory group (11.4%) was similar to that in the not taxane refractory group (13.1%).

Irrespective of the sponsor's arguments justifying eribulin treatment in taxane refractor patients, it is considered that it would be difficult to defend denying treatment with eribulin to taxane refractory patients based on the data from an underpowered, post hoc, subgroup analysis.

7.1.4.2.2. OS by TPC group

The submission included a number of other p*ost-hoc* analyses based on the pivotal study comparing OS in the eribulin and TPC groups. The result of these analyses will not be discussed in this evaluation report as they are not considered to be relevant as regards the recommendation to accept or reject the submission.

7.2. Other efficacy studies

7.2.1. Study 211 (Phase II, open-label, single-arm)

7.2.1.1. Study design, objectives, locations and dates

This study was a Phase II, multi-national (USA and the EU), multi-centre, open-label, single-arm, trial in breast cancer patients who had received at least two, and not more than five, prior chemotherapy regimens for the treatment of their disease. Prior chemotherapy was to include an anthracycline, a taxane, and capecitabine, which may have been administered in any combination or order. In addition, the inclusion criteria required that patients with HER2/*neu* over-expressing tumors must have been treated with trastuzumab. Up to two prior regimens for adjuvant treatment were allowed, but at least one regimen must have been for advanced disease. Patients were to have progressed or relapsed within 6 months of their last chemotherapy regimen for advanced disease. There were four amendments made to the study protocol. These have been examined and are considered not to have compromised the validity of the study. Data from the study have been reported in two publications.[5, 6]

The *primary objective* was the evaluation of the efficacy and safety of eribulin patients with locally advanced or metastatic breast cancer who had received anthracycline, taxane, and capecitabine as prior therapy, and were refractory to their last chemotherapy regimen, documented by progression on or within 6 months of therapy. The *secondary objective* was to investigate the PK/PD relationships in a population-PK.

The study was conducted from 28 October 2005 (first patient in) through to 1 September 2007 (data cut-off), and the date of the CSR report was 25 February 2010. The studied complied with the ethical and good clinical practice principles required by the TGA.

[5] Vahdat LT, Twelves C, Allison MK, et al. Phase II study of eribulin mesylate (E7389) in patients (pts) with locally advanced or metastatic breast cancer (MBC) previously treated with anthracycline, taxane, and capecitabine therapy. J Clin Oncol. 2008;26 (May 20 Suppl;abstr 1084).

[6] Cortes JA, Campone M, Twelves C, et al. Eribulin mesylate (E7389) in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane: Phase II neuropathy data. Proceedings of the 33rd ESMO Congress, Stockholm, Sweden. Ann Oncol. 2008;19 Suppl 8:viii70.

7.2.1.1.1. Inclusion and exclusion criteria

Female patients aged ≥ 18 years who satisfied all the *inclusion and exclusion* were eligible for entry.

7.2.1.1.2. Study treatments

Eribulin was administered as an iv bolus 1.4 mg/m^2 over 2-5 minutes on Days 1 and 8 every 21 days. The protocol allowed for dose modification based on toxicities. The dose modification protocol was consistent with that for the pivotal Phase III study [305]. Patients continued in the study until they had unacceptable toxicity or progression of disease, or until the investigator determined that discontinuation of therapy was in the best interest of the patient. Patients who demonstrated clinical benefit were allowed to continue treatment for as long as clinical benefit was sustained. Prior and concomitant therapies were similar to those for the pivotal, Phase III study [305]. The median number of cycles of eribulin received per patient was 4 [range 1 to 27], the median dose intensity was 0.86 mg/m^2/week, and the median duration of exposure was 84 days.

7.2.1.1.3. Efficacy variables and outcomes

The *primary efficacy endpoint* was the objective overall response rate (ORR), defined as the number of patients with a best overall response (CR or PR) divided by the number of patients in the eligible population. The *secondary endpoint* was duration of response (DoR). Other *additional endpoints* were overall survival (OS) and progression-free survival (PFS).

DoR was defined as the time from first documented CR or PR until disease progression or death from any cause. It was measured from the time that measurement criteria were met for CR or PR (whichever status is recorded first) until the first date that recurrent disease or progressive (PD) was objectively documented. A patient's duration of response was censored at the last date of tumor assessment if treatment was discontinued for a reason other than PD or death, if the patient started a new cancer treatment, or if the patient was still on treatment without PD as of the data cut-off date (1 September 2007).

OS was defined as the time from the start of study drug administration until death from any cause. *PFS* was defined as the time from start of study drug administration until PD or death from any cause during the study period in the absence of disease progression. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the data cut-off date (1 September 2007) were censored at that date.

Tumor response and progression were evaluated using RECIST criteria. Tumor assessments were performed at each study site based upon the local radiology report. Clinical management of patients was based upon this assessment. To maintain uniformity of tumor assessments across study sites, an independent review of radiographic images involving two radiologists was also performed for all treated patients, except those determined by study investigators to have progressed on or before their Cycle 2 scan. Imaging for independent review included all available CT, MRI and bone scans. The results of both investigator and independent assessments were analysed. For the primary efficacy analysis the results of the independent review superseded in cases of discordance.

7.2.1.1.4. Randomisation and blinding methods

This was an open label study involving one treatment group (eribulin mesylate). Consequently, the study was not blinded and patients were not randomised.

7.2.1.1.5. Analysis populations

The *intent to treat (ITT)* population consisted of all patients who received at least one dose of study treatment. The *safety population* was the same as the ITT population. The *eligible population* consisted of patients who received at least one dose of therapy and met specified criteria consisting of the first three inclusion criteria, with eligibility additionally validated by an

independent review committee consisting of eight breast cancer experts. The purpose of independent review was to ensure the population used for assessment of the activity of eribulin in this single arm study was appropriate. The eligible population represents a patient population that has received the standard of care for breast cancer and is representative of a refractory population. The eligible population was used for the primary analysis.

7.2.1.1.6. Sample size

Up to a maximum of 300 patients were planned to be enrolled in this study. It was determined that a sample size of 250 eligible patients would be sufficient to detect a difference in response rate of 8% (15% null hypothesis rate, 23% alternative hypothesis rate) with 88% power, based on a binomial test with a nominal 0.025 one-sided significance level. A sample size of 250 patients would be sufficient to detect a 9% difference (15% null hypothesis rate, 24% alternative hypothesis rate) with 94% power, based on a 0.025 one-sided test.

7.2.1.1.7. Statistical methods

The primary analysis of the eligible population was based on the best overall response as determined by the independent review. The null hypothesis (H_0) was ORR ≤ 15% on the eligible population tested, one-sided 0.25 significance level; the alternative hypothesis (Ha) was ORR >15% on the eligible population tested, one-sided 0.25 significance level. For the eligible population, if the null hypothesis was rejected at the 0.025 level or the Pearson-Clopper 2-sided 95% CI of the ORR was found to be above 15%, then eribulin treatment would be deemed efficacious in this population.

The ORR based on the results of independent review was evaluated in a number of pre-specified subgroups. In addition, the ORR in the chemotherapy refractory sub-populations was evaluated using four alternate definitions of refractoriness. For each subgroup, the number and percentage of patients assigned to each category (CR, PR, SD, PD, and Not Evaluable [NE]) were summarised and the response rate was estimated together with an exact Pearson-Clopper 2-sided 95% CI. In addition, summaries were provided for the ITT population. Similar analyses were performed using the investigators' assessment on both eligible and ITT populations.

The DoR, PFS, and OS analyses were performed on both the ITT and the eligible populations. The eligible population was considered the primary population for analysis of these endpoints. DoR was analyzed by both independent reviewer and investigator assessments separately using appropriate censoring rules. DoR, PFS, and OS were summarised using Kaplan-Meier methods. Median and the 95% CIs were provided. For the independent review, in cases where tumor response assessments were performed after clinical progression, a sensitivity analysis was performed by taking clinical progression into account.

7.2.1.1.8. Participant flow

A total of 299 of the planned 300 patients were enrolled (data were not available for 1 patient due to medical records being lost), and a total 291 patients (ITT/safety population) were treated with eribulin. The eligible population included 269 patients. Of the 298 enrolled patients with available data, 295 (99.0%) had discontinued and 3 (1.0%) were ongoing at the data cut-off date. The majority of patients discontinued the study due to progressive disease according to RECIST criteria (212, 71.1%). Other reasons for study discontinuation were AEs (25, 8.4%), clinical progression (11, 3.7%), physician's decision (11, 3.7%), patient withdrew consent (7, 2.3%), and "other" (10, 3.4%). No patients were lost to follow-up. Death occurred in 12 (4.0%) patients during the study treatment or within 30 days after the last study treatment.

7.2.1.1.9. Major protocol violations/deviations

There were 22 treatment administration deviations, 16 patient eligibility deviations, and 2 concomitant medication deviations.

7.2.1.1.10. Baseline data

The mean (SD) age of the eligible population (n=269) was 55.4 (11.0) years and the range was 26 to 80 years. The majority of patients were aged 18-64 years (217, 80.7%). The majority of patients were white (187, 69.5%), but there were a significant number of patients for whom information on race was missing (57, 21.2%). A summary of selected baseline breast cancer disease characteristics (ITT/safety population), and a summary of prior chemotherapy (ITT/safety population) was provided in the submission.

7.2.1.2. Results

The efficacy results from the independent review in the eligible population are summarised below in Table 23.

Table 23: Efficacy results (independent review); eligible population (n=269).

ORR	Primary endpoint	9.3% [95% CI: 6.1, 13.4%]; p=0.996; 25/269 patients.
DoR	Secondary endpoint	126 days median [95% CI: 89, 177]; patients died or progressed / censored = 16/9.
PFS	Additional endpoint	79 days median [95% CI: 64, 92]; patients died or progressed / censored = 220/49.
OS	Additional endpoint	315 days median [95% CI: 279, 350]; patients died / censored = 170/99.

Notes: ORR = Objective Response Rate; DoR = Duration of Response; PFS = Progression Free Survival; OS = Overall Survival.

The ORR (independent review) in the eligible population consisted of no patients with a CR and 25 (9.3%) patients with a PR. The ORR (investigator review) in the eligible population (n=269) was 14.1% [95% CI: 10.2, 18.9]; p=0.656. The ORR (investigator review) in the eligible population included a total of 38 patients (1 CR, 37 PR).

In the subgroup analyses of the ORR (independent review) in the eligible population, the only two subgroups with a response rate ≥ 15% were obese and postmenopausal women (17.2%, 5/29), and women with a histological diagnosis of lobular adenocarcinoma of the breast (18.2%, 4/22). No meaningful conclusions can be drawn from these analyses given the small patient numbers in the subgroups and the absence of a control comparator.

> **Comment:** In study 211, the ORR determined by independent review in the eligible population was 9.3% [95% CI: 6.1, 13.4]; p=0.996. In this adequately powered study the null hypothesis was not rejected as the ORR was ≤ 15%. The baseline demographic and disease characteristics of the study population in study 211 were generally consistent with those in pivotal study 305. However, in study 211 all patients were required to have been previously treated with capecitabine compared with study 305 where this was not a requirement. In addition, in study 211 patients with HER2/*neu* over-expressing tumors must have been treated with trastuzumab while this was not a mandatory requirement for patients in the pivotal study 305.

7.2.2. Study 201 (Phase II, open-label, single-arm)

7.2.2.1. Study design, objectives, locations and dates

This study was a Phase II, US, multi-centre (23 centres), open-label, single-arm trial in patients with advanced/metastatic breast cancer previously treated with chemotherapy including an anthracycline and a taxane with previously documented progression during or within 6 months

following the last dose of prior chemotherapy. Data from the study have been reported in published abstracts.[7, 8, 9]

The *primary objective* was to determine the response rate to eribulin monotherapy at a dose of 1.4 mg/m^2 administered as an iv bolus on Days 1, 8, and 15 of a 28-day cycle and on Days 1 and 8 of a 21-day cycle in patients with advanced/metastatic breast cancer treated with chemotherapy including an anthracycline and a taxane with previously documented progression during or within 6 months following the last dose of prior chemotherapy.

The *secondary objectives* were to evaluate: (1) the safety and tolerability of the administered eribulin mesylate treatment regimens; (2) the antitumor activity of eribulin as determined by duration of response (DoR), progression free survival (PFS), and overall survival (OS); (3) the quality of life (QOL) measured by the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire, tumor-related symptom improvement or worsening measured by pain intensity on a visual analog scale (VAS), analgesics consumption, weight changes and Eastern Cooperative Oncology Group (ECOG) performance status; and (4) tumour pharmacogenetics and their possible relationship to response (assessment of beta-tubulin isotype mRNA on biopsy sample).

The study was conducted from 12 November 2004 to 1 November 2006, and the date of the CSR was 12 February 2010. The studied complied with the ethical and good clinical practice principles required by the TGA.

7.2.2.1.1. Inclusion and exclusion criteria

Female patients aged ≥ 18 years who satisfied all the inclusion and exclusion were eligible for entry. The study included standard criteria for withdrawing patients from the study (i.e., withdrawal of consent; pregnancy; use of prohibited concomitant treatment; non-compliance with the protocol; and investigator/sponsor decision to remove the patient from the study for administrative or other reasons).

7.2.2.1.2. Study treatments

In this study, enrolment was based on Simon's optimal two stage design.[10] During Stage I of patient enrolment, eribulin was to be tested on 19 evaluable patients. If less than 2 patients showed CR or PR the study was to be terminated. If there were at least 3 responders in Stage I, an additional 42 evaluable patients (a planned total of 61) were to be enrolled during Stage II. A second cohort of 25 evaluable patients was added to the study when it became apparent that the treatment schedule needed to be revised due to neutropenia precluding treatment on Day 15 in many patients.

The first cohort of patients (61 planned, 71 enrolled) received eribulin at a dose of 1.4 mg/m^2 as an iv bolus on Days 1, 8, and 15 of a 28-day cycle. The second cohort of patients (25 planned, 33 enrolled) received eribulin at a dose of 1.4 mg/m^2 as an iv bolus on Days 1 and 8 of a 21-day cycle. The protocol allowed for dose modification and/or cessation based on haematological and non-haematological toxicities. The assessment schedule for the second cohort who received the treatment regimen proposed for approval was provided in the dossier.

Patients remained on study treatment until objective progressive disease had occurred, clinical benefit was no longer evident, or unacceptable toxicity resulting in study withdrawal had

[7] Blum J, Forero L, Heiskala MK, Meneses N, Chandrawansa K, Fang F, Shapiro G, Silberman S, Vahdat L. E7389, a novel anti-tubulin, in patients with refractory breast cancer. ASCO Annual Meeting 24; 2006:No 18S, Abstract 653.
[8] Blum JL, Pruitt B, Fabian CJ, Rivera RR, Shuster DE, Meneses NL, et al. Phase II study of eribulin mesylate (E7389) halichondrin B analog inpatients with refractory breast cancer. ASCO Annual Meeting 25; 2007:No. 18S, Abstract 1034.
[9] Blum JL, Pruitt BT, Fabian CJ, Shuster DE, Meneses NL, Chandrawansa K, Fang F, Vahdat L. Phase II study of eribulin mesylate (E7389) in patients with heavily pretreated advanced breast cancer. ASCO BSC; 2007:Abstract 223.
[10] Simon R. Optimal two-stage designs for Phase II clinical trials. Controlled Clinical Trials. March 1989;10:1-10.

occurred (toxicity requiring three permanent dose reductions or cycle delay of ≥ 6 weeks). Prior and concomitant therapies were similar to those for the pivotal study [305].

7.2.2.1.3. Efficacy variables and outcomes

The *primary efficacy endpoint* (which was also the primary efficacy variable) was the overall response rate (ORR), defined as CR or PR confirmed 4 to 8 weeks after first observed. The *secondary efficacy endpoints* were duration of response (DoR), progression free survival (PFS), and overall survival (OS). Definitions of the efficacy endpoints were similar to those for studies 305 and 211.

Tumor response and progression were evaluated using the RECIST Criteria. To maintain uniformity of tumor assessment, an independent, blinded review of radiographic images was also performed for all patients, except those determined by study investigators to have progression on or before their Cycle 2 scan. The results of the independent review superseded in cases of discordance. The definition of target and non-target lesions were the same as used in studies 305 and 211, as were the definitions of response.

7.2.2.1.4. Randomisation and blinding methods

This open-label, single-arm study was not randomised or blinded. Patients were assigned to treatment groups based on the order of enrolment in the first and second cohorts.

7.2.2.1.5. Analysis populations

The intent to treat (ITT) population consisted of all patients who received at least one dose of study treatment. The *safety population* was the same as the ITT population. The *evaluable population* consisted of patients who completed at least one cycle of treatment according to the protocol, or who discontinued during the first cycle due to PD or death. This population was planned to be the primary analysis population for the efficacy analysis.

> **Comment:** The primary efficacy analysis was planned to be performed on the evaluable population, which included all patients who completed at least one cycle of treatment according to the protocol, or who discontinued during the first cycle due to PD or death. However, this criterion for inclusion in the analysis population was removed, so that no patients were excluded for not completing a full cycle of treatment. The primary efficacy analysis population was further modified when it was determined that 16 patients did not meet key inclusion criteria relating to disease progression within 6 months of prior chemotherapy or having measurable disease. Therefore, a modified population ("per-protocol" [PP]) which included only those patients who met these key enrolment criteria was used for the primary efficacy analysis.

7.2.2.1.6. Sample size

The Simon's optimal two-stage design to test the null hypothesis (i.e. H0: RR ≤ 0.12) versus the alternative hypothesis (i.e. Ha: RR ≥ 0.25) had an expected sample size of 35.94 subjects and a probability of early termination of 0.597. If the drug is actually not effective, there is a 0.048 probability of concluding that it is (the target was 0.050). If the drug is actually effective, there is 0.0197 probability of concluding that it is not (the target was 0.200). It was determined that 61 evaluable patients would be sufficient to demonstrate the efficacy of the 28-day cycle treatment regimen.

Enrolment of the 61 evaluable patients in the 28-day cycle regimen was planned to take place in two stages. In Stage I, eribulin was to be tested in 19 patients. If ≤ 2 patients responded (i.e. CR + PR) the trial was to be terminated, unless clinical judgment suggested otherwise. In Stage II, if there were ≥ 3 responders in Stage I, an additional 42 patients (giving a total of 61) were to be enrolled. If total responders (Stage I + Stage II) were ≤ 11 patients, efficacy of the 28-day cycle for the indication was be rejected, unless clinical judgment suggested otherwise.

In a protocol amendment (Amendment 01), a second group of 25 evaluable patients was to be enrolled to receive the 21-day cycle regimen. The addition of this second cohort followed the observation that a notable number of dose interruptions, delays, reductions, and omissions were needed during the first two cycles of the 28-day cycle regimen (63% of patients in cycle 1 and 54% of patients in cycle 2). The 21-day cycle regimen was better tolerated than the 28-day cycle regimen resulting in as third as many treatment disruptions in the first cycle and as fifth as many during the second cycle. The same eligibility criteria and evaluations applied to the cohort second cohort as applied to the first cohort.

7.2.2.1.7. Statistical methods

The *primary analysis of the primary efficacy endpoint* of ORR was from the independent review with the secondary analysis being from the investigator review. A two-sided 95% confidence interval for the ORR was calculated using binomial distribution. Summaries were provided for both ITT and evaluable populations. The *secondary endpoints* of DoR, PFS, and OS were analyzed using Kaplan-Meier methods, and the median (including the 95% CI) were estimated. Summary statistics were provided separately for both the 28-day and 21-day cohorts. However, only the efficacy results from the 21-day cohort will be reviewed in this evaluation report.

> **Comment:** As discussed above a PP population was defined because of modifications to the evaluable patient population, primarily due to significant protocol violations relating to inclusion criteria. The PP consisted of 87 patients (59 in the 28-day regimen; 28 in the 21-day regimen).

7.2.2.1.8. Participant flow

A total of 104 patients were enrolled in the study (71 in the 28-day regimen, 33 in the 21-day regimen). The evaluable patient population included 102 patients (69 in the 28-day regime and 33 in the 39 day regimen).

7.2.2.1.9. Major protocol violations/deviations

There were 74 important protocol deviations in 104 patients. The 74 protocol deviations consisted of 36 treatment administration, 17 patient eligibility, 14 concomitant therapy, 5 tumour assessment, and 2 treatment discontinuations. Treatment administrations were sometimes delayed due to toxicity, illness, or physician or patient schedules. Treatments were not always given as an iv bolus within 5 minutes as specified in the protocol, and some infusions lasted longer than 10 minutes. Of the 104 patients with an important protocol deviation, 13 were related to disease which did not progress within 6 months of last prior chemotherapy and 3 had no measurable disease on or within 6 months of last prior chemotherapy. The 16 patients who violated one or other of these two criteria were excluded from the primary efficacy analysis. Data for the other 88 patients with important protocol deviations were not excluded from the statistical analysis.

7.2.2.1.10. Baseline data

The mean (SD) age of the total ITT/safety population (n=103) was 55.4 (10.8) years and the range was 32 to 84 years. The majority of patients in this population were aged 18-64 years (80, 77.7%).The majority of patients in this population were white (72, 69.9%), followed by hispanic (12, 11.7%), black (11, 10.7%), Asian/pacific (5, 4.9%) and other (3, 2.9%). The basic demographic data were similar in the 28 and 21-day treatment regimens.

The median time since original diagnosis in the total safety population (n=103) was 67.4 months [range 6.4 to 240.3]. In the total safety population (n=103), the majority of patients had ECOG status 1 (47, 54.4%), were ER positive (63, 61.2%), were PgR negative (53, 51.5%), and were HER2/*neu* negative (82, 79.6%). Of the total safety population, 29.1% (n=30) were negative for ER, PgR and HER2/*neu*. There were no marked differences between the 28 and 21-day treatment regimens as regards the baseline disease characteristics / status.

In the total safety population (n=103) most patients had received prior hormonal therapy (60, 58%), while prior trastuzumab therapy had been received by 26 (25%) patients. The median number of prior chemotherapy regimens was 4, and 32 (31.1%) patients had received 6-11 prior regimens. All patients had been treated with prior anthracyclines and taxanes, 68.0% (n=11) had been treated with prior capecitabine, 45.5% (n=47) with prior vinorelbine, and 55.3% (n=57) with prior gemcitabine. The median duration of the last chemotherapy in the safety population was 2.4 months [range 0.03 to 25.0], and the median time from last chemotherapy to first dose of eribulin was 1.2 months [range 0.5 to 93.3 months]. Overall, prior anti-cancer therapy was similar in the 28 and 21-day treatment regimens.

A total of 103 patients received treatment during the study (70 patients in the 28-day treatment group and 33 patients in the 21-day treatment group). The median (range) number of cycles received per patient was 2.5 (1-18 cycles) and four (1-21 cycles), respectively, for patients in the 28-day and 21-day treatment groups. The median dose intensity was 0.74 mg/m^2/week and 0.85 mg/m^2/week for patients in the 28-day and 21-day treatment groups, respectively.

7.2.2.2. Results

The results from the independent review of the efficacy endpoints in the ITT population are summarised below in Table 24.

Table 24: Study 211 – Efficacy results (independent review); per-protocol population (28-day [n=59] and 21-day [n=28]).

ORR	Primary endpoint	28-day: 10.2% [95% CI: 3.8, 20.8]; patients 6/59 21-day: 14.3% [95% CI: 4.0, 32.7]; patients 4/28
DoR	Secondary endpoint	28-day: 153 days [95% CI: 114, 363]; patients progressed or died/censored = 5/1 21-day: only 1 patient progressed or died; patients progressed or died/censored = 1/3
PFS	Secondary endpoint	28-day: median 57 days [95% CI: 51, 107]; patients progressed or died/censored = 45/14 21-day: median 86 days [95% CI: 76, 246]; patients progressed or died/censored = 18/10
OS	Secondary endpoint	28-day: median 239 days [95% CI: 191, 379]; patients died/censored = 48/11. 21-day: - ; patients died/censored = 13/15; 6 month and 1 year survival, 71.4% & 60.7%, respectively

Notes: ORR = Overall Response Rate; DoR = Duration of Response; PFS = Progression Free Survival; OS = Overall Survival.

In the independent review (PP population), the ORR in the 28-day regimen consisted of no patients with CR and 6 patients with PR, and the ORR in the 21-day regimen consisted of no patients with CR and 4 patients with PR. The ORR in the total PP population (n=87) was 11.5% (10/87) [95% CI: 5.7, 20.1], consisting of no patients with CR and 10 patients with PR.

> **Comment:** The protocol specified primary analysis in the evaluable population could not be undertaken due to the relatively large number of patients (n=16) with significant protocol violations relating to inclusion criterion 5 (i.e., patients must have progressed within 6 months of the last dose of chemotherapy, or experienced disease progression while receiving chemotherapy for advanced/metastatic disease), or inclusion criterion 3 (i.e., patients must have measurable disease by RECIST); 13 and 3 violations, respectively. Consequently, no formal assessment against the pre-specified statistical efficacy assessment could be made. The ORR for the 21-day treatment regimen was greater than

for the 28-day treatment regimen, but the 95% CI was notably wider in the 21-day compared with the 28-day regimen which probably reflects the smaller sample size.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

The Summary of Clinical Efficacy [Module 2.7.3] included a descriptive analysis of the pooled efficacy data from studies 305, 211, and 201. The relevant efficacy data from this analysis have been provided in this evaluation report primarily for information. The analysis provides limited supportive evidence for the efficacy of eribulin for the proposed indication due to the absence of comparator treatment. In particular, pooling of OS and PFS was not considered meaningful due to the lack of a comparator arm. Therefore, the main efficacy data in the descriptive pooled analysis (eribulin treated patients) were the overall response rate (ORR), duration of response (DoR), clinical benefit rate (CBR), and disease control rate (DCR).

Studies 211 and 201 recruited female patients with locally recurrent breast cancer (LRBC) or metastatic breast cancer (MBC) who had been previously treated with an anthracycline and a taxane. Study 305 recruited female patients with LRBC or MBC who had been previously treated with two to five chemotherapy regimens, which again must have included an anthracycline and a taxane (unless contraindicated). For all three studies, in this pooled analysis disease must have progressed or relapsed within six months of the last chemotherapy regimen.

The main differences in inclusion criteria between the three studies were: study 211 required patients to have received prior capecitabine therapy, in addition to prior anthracycline and taxane therapy, while studies 201 and 305 did not require prior capecitabine therapy; studies 211 and 305 required at least two and no more than five prior chemotherapy regimens (not counting hormonal, biological, or immunological therapies), while study 201 did not limit the number of prior chemotherapy regimens; patients in study 211 must have received at least one prior chemotherapy regimen for LRBC or MBC, while patients in study 305 must have received at least two prior chemotherapy regimens for advanced disease and patients in study 201 did not require a prior regimen for advanced disease; patients in study 211 with HER2/*neu* over-expressing tumors must have been treated with trastuzumab, but there was no such requirement in studies 201 and 305; and study 201 required patients to have an ECOG performance status of 0 or 1, while ECOG performance status for patients in studies 211 or 305 could be 0, 1 or 2.

Data from the pivotal Phase III study [305] and the two Phase II studies [211, 201] were pooled for those patients who received at least one dose of eribulin according to the proposed dosing regimen Consequently, the data from the 28-day cycle regimen in study 201 were excluded. For study 305, patients who actually received eribulin were included (described as Eribulin-Treated [ET]) (N=503). This population differs from the primary analysis for study 305 which was in the ITT population defined as patients who were randomised to each treatment group (eribulin or TPC), irrespective of treatment actually received (N=508).

The pooled data analysis included a comparison between two eribulin treated patient groups : (1) a total of 827 patients from study 201 (21-day cycle; N=33) + study 211 (N=291) + plus ET patients from study 305 (N=503); and (2) a total of 503 ET patients from study 301. The sponsor stated that pooling of the Phase II/III studies allowed improved point estimates relative to the Phase III study alone. The results for the OR, DoR, CBR, and DCR in the eribulin treated population are summarised below in Table 25.

Table 25: Comparison between pooled PII/PIII and PIII efficacy data, independent review, eribulin treated patients.

ORR	PII/PIII (n=827) PIII (n=503)	10.8% (89/827) [95% CI: 8.7, 13.1]; CR = 3 and PR = 86 11.3% (57/503) [95% CI: 8.7, 14.4]; CR = 3 and PR = 54.
DoR	PII/PIII (n=89) PIII (n=57)	142 days median [95% CI: 126, 168]; patients progressed or died / censored = 49 /40 145 days median [95% CI: 125, 176]; patients progressed or died / censored = 31 /26
CBR	PII/III (827) PIII (n=503)	20.6% (170/127) [95% CI: 17.9, 23.5] 22.9% (115/203) [95% CI: 19.3, 26.8)
DCR	PII/III (827) PIII (n=503)	54.3% (449/827) [95% CI : 50.8, 57.7] 52.9% (266/503) [95% CI: 48.4, 57.3]

Notes: PII/PPP = pooled results from Phase II (211 and 201 [21-day treatment cycle only) and Phase III study (305 eribulin treated patients only). If a patient was not independently reviewed, then the investigator's response was used. ORR = observed odds ratio (complete response [CR] + partial response [PR]; 95% exact 2-sided test. DoR = duration of response. CBR = clinical benefit rate (CR + PR + SD [stable disease ≥ 6 months]); 95% exact 2-sided test. DCR = disease control rate (CR + PR + SD); 95% exact 2-sided test.

The data also included descriptive analyses of the ORR, CBR, and DCR in the pooled Phase II/III eribulin treated population (independent review) comparing outcomes in demographic subgroups, hormone and HER2/*neu* expression subgroups, disease history subgroups. disease duration subgroups, concurrent disease subgroups, prior drug treatment subgroups, prior refractory subgroups, prior hormonal subgroups, and dose modification subgroups. None of the subgroup analyses included a control comparator. The results from these analyses are exploratory and are considered not relevant to the decision whether or not to approve eribulin for the proposed indication.

7.4. Evaluator's conclusions on clinical efficacy for the proposed indication

The submission included one, pivotal, Phase III, open-label study [305] that compared the effect of eribulin (n=508) administered at the proposed dosing regimen with TPC (n=254) on the primary efficacy variable of OS, and the secondary efficacy variables of PFS, ORR, and DoR in women with heavily pre-treated metastatic breast cancer. Overall, the patient population in the pivotal study is considered to reflect both the patient population specified in the proposed indication, and women in the Australian community who might be offered treatment with eribulin.

The submission also included two, Phase II, open-label, one-arm studies [201, 211] in which the primary efficacy endpoint was the ORR and the secondary efficacy endpoints were OS, PFS, and DoR. In addition, the submission included a descriptive analysis of the pooled efficacy data from the two Phase II studies [201, 211] and the single, pivotal Phase III study [305]. However, the two Phase II studies and the pooled Phase II/III analysis provide limited efficacy data which are difficult to interpret in the absence of a control comparator. In particular, data from the key efficacy endpoints of OS and PFS are not considered to be clinically meaningful in the absence of a suitable comparator. Consequently, it is considered that the efficacy data supporting the submission are dependent on the single, pivotal, Phase III study.

The pivotal study [305] showed that the primary efficacy endpoint of OS (ITT population) in patients in the eribulin group (n=508) was statistically significantly superior compared with

patients in the TPC group (n=254). In the original data, the median OS was 399 days [95% CI: 360, 434] in the eribulin group and 324 days [95% CI: 282, 380] in the TPC group: HR = 0.809 [95% CI: 0.660, 0.991]; p=0.041, stratified log-rank test. Since there was an interim analysis, the adjusted significance level for the final log-rank test was 0.049. The OS analysis in the PP population showed a numerically similar HR to the OS analysis in the ITT population, but in contrast to the ITT analysis the PP analysis was not statistically significant. The failure of the PP analysis to demonstrate statistical significance was probably due to the small sample size.

The results for OS survival in the original analysis were confirmed in the updated analysis (ITT population) which included more mature data: i.e., a total of 589 deaths (77.3% of enrolled patients) in the updated data compared with 422 deaths (55.4% of enrolled patients) in the original data. In the updated data, the median OS was 403 days [95% CI: 367, 438] in the eribulin group (n=508) and 321 days [95% CI: 282, 365] in the TPC group (n=254): HR = 0.805 [95% CI: 281, 365]; p=0.014, stratified log-rank test. In the updated data, the OS analysis in the PP population was statistically significant.

In the original analysis, the median OS benefit in the ITT population in favour of eribulin compared with TPC was 75.0 days [95% CI: 21.4, 128.6]. This result is consistent with the updated analysis which showed a median OS benefit in favour of eribulin compared with TPC of 82 days [95% CI: 29.9, 134.1]. The median OS of benefits in favour of eribulin of 75 days and 82 days (i.e., 2.5 months and 2.7 months) are considered to be clinically meaningful in the population of women studied in the pivotal study. However, it should be noted that the assumptions made to estimate the sample size included median overall survivals of 9 months and 12 months in the TPC and eribulin groups, respectively (i.e., a hazard ratio of 0.75). These assumptions suggest that the minimal clinically significant median OS benefit in favour of eribulin relative to TPC was considered by the sponsor to be 3 months. Neither the original nor the updated OS benefits for eribulin relative to TPC quite reached the 3 month value.

There were no updated PFS data and all results relate to the original data. Median PFS (ITT population) was 45 days longer in the eribulin group compared with the TPC group, although the difference did not reach statistical significance based on blinded Independent review (primary analysis): HR = 0.865 [95% CI: 0.714, 1.048]; p=0.137, stratified log-rank test). In this analysis, the median PFS was 113 days and 68 days in the eribulin group and TPC group, respectively. However, in a sensitivity analysis based on Investigator review the median PFS (ITT population) was 44 days longer in the eribulin group compared with the TPC group, and the difference between the two treatment groups (110 and 66 days, eribulin and TPC, respectively) was statistically significant: HR = 0.757 [95% CI: 0.638, 0.900]; p=0.002. The difference in statistical significance between the two reviews relate to different censoring rules relating to disease progression in the Independent review compared with the Investigator review. However, despite the difference in statistical significance between the two reviews, the numerical median PFS benefits in the eribulin group compared with the TPC are considered to be clinically equivalent (i.e., 45 and 45 days, Independent and Investigator, respectively).

There were no updated ORR data and the results relate to the original data. Based on the Independent review in the response evaluable population, the ORR was 12.2% [95% CI: 9.4, 15.5] in the eribulin group and 4.7% [95% CI: 2.3, 8.4] in the TPC group: p=0.002, Fisher's exact test. The major contributor to the ORR in both treatment groups was PR (11.5% and 4.7%, eribulin and TPC groups, respectively), with CR being 0.6% in the eribulin group and 0% in the TPC group. There were no updated DoR data and the results relate to the original data. In the Independent review, there was no statistically significant difference between the two treatment groups, but the TPC group is considered to include too few patients to make the comparison meaningful.

There were a number of pre-specified and *post hoc* subgroup analyses of OS in the pivotal study. It is considered that these analyses are exploratory. The study was not designed to test the subgroup comparisons, none of the subgroup comparisons were specified as primary or

secondary efficacy variables, the subgroup analyses were underpowered, and no statistical adjustments were made to account for the multiple pairwise comparisons.

In summary, the current submission is considered to provide relevant efficacy data from only one pivotal Phase III study [305], with the supportive efficacy data from the two Phase II studies [201, 211] and the pooled Phase II/III studies [305, 201, 211] providing only limited information due to the lack of control comparator treatment (particularly relating to OS and PFS). The TGA has adopted an EU guideline which provides guidance on applications with one pivotal study [Points to Consider CPMP/EWP/2330/99]. The "points to consider" document states that there is a "general demand for replication of scientific results", but notes that "clinical drug development differs from the situation with strictly experimental studies". However, the document states that where the confirmatory evidence is provided by only one pivotal study then the study will have to be "exceptionally compelling", and the regulatory evaluation will need to pay special attention to certain factors.

If the factors listed in the "points to consider" document are applied to the pivotal Phase III study [305] in the current submission then the following observations can be made: the study is considered to be internally valid and no significant potential biases have been identified even though the study is open-label and the comparator is a mixture primarily of chemotherapy treatments of physicians' choice; the study is considered to be externally valid as the results can be reasonably extrapolated to an Australian population of women with locally recurrent or metastatic breast cancer previously treated with chemotherapy as defined by the proposed indication; the increase in median OS of 2.7 months (updated data) in the eribulin group compared with the TPC group is considered to be clinically relevant in the proposed patient population; the degree of statistical significance for the primary efficacy endpoint of OS for the comparison between eribulin and TPC is considered to be satisfactory for both the original and updated data; the data quality is considered to be good; there is internal consistency between the key efficacy endpoints of OS and PFS with both time-to-event efficacy variables being longer in the eribulin group compared with the TPC group; there were no reported centre effects although subgroup analysis based on geographical regions showed a statistically significant OS benefit in eribulin treated patients compared with TPC in Region 1 (North America/Western Europe/Australia) but not in Region 2 (Eastern Europe) or Region 3 (Latin America/South Africa); and the plausibility of the hypothesis tested is considered reasonable given that eribulin has in *vivo* activity against a range of tumour types including human breast cancer xenografts.

8. Clinical safety

8.1. Studies providing evaluable safety data

The primary focus of the review of the safety data in this clinical evaluation report is on the comparison between eribulin and TPC from the pivotal Phase III study [305]. The data from the pivotal study are the only safety data in the submission which compared eribulin administered at the proposed dose regimen for the proposed indication with a comparator group. In the pivotal study, the safety population consisted of all randomised patients who received at least a partial dose of study treatment. It included a total of 750 patients of whom 503 were in the eribulin group and 247 were in the TPC group.

The primary safety data from the pivotal Phase III study [305] are supported by pooled safety data from 1222 eribulin treated patients from 11 completed Phase I/II/III studies [studies 305, 201, 202, 204, 211, 201, 102, 103, 108, 109, 110]. The 1222 patients in the PI/II/III all eribulin treated population (AETP) included a Breast Cancer Population (BCP) of 827 patients from 2 Phase II studies [201, 211] and 1 pivotal Phase III study [305] who had been treated with eribulin at the proposed dose. In addition to the 827 patients with breast cancer from the 3 PII/PIII studies [201, 211, 305], the AETP included a total of 395 patients from 8 other

completed Phase I/II studies in solid tumours, including 70 patients with breast cancer treated with eribulin according to the 28-day schedule in Study 201. The 11 Phase I/II studies (apart from studies 201, 211, and 305) included: 2 completed Phase 1 dose-escalation studies [101, 102]; 4 completed Phase 1 clinical pharmacology studies [103, 108, 109, 110]; and 2 completed Phase II studies ([202 [NSCLC], 204 [advanced prostate cancer] with a data cut-off of 31 May 2009. In general, safety in each clinical study was assessed by treatment emergent adverse events (TEAEs), serious TEAEs, deaths, extent of exposure to study treatment, physical examination findings, vital sign measurements, ECGs, and clinical laboratory results.

There was considerable overlap among eribulin treated patients from the pivotal study (n=503), the AETP group (n=1222), and the BCP group (n=827). Of the 1222 patients in the AETP group, 67.7% (n=827) came from the BCP group, and of these 827 patients 60.8% (n=503) came from eribulin treated patients in the pivotal study. Baseline demographics, disease characteristics and prior cancer treatments for the AETP are provided in the submission. Patient disposition in the relative eribulin treated groups are summarised below in Table 26.

Table 26: Patient disposition AETP (n=1245), BCP (n=840) and pivotal study (n=752); all enrolled patients.

	Eribulin Treated Patients PI/II/III		Pivotal PIII study 305	
	All (AETP)	Breast Cancer (BCP)	Eribulin	TPC
Enrolled	1245	840	508	254
Treated	1222 (98.2%)	827 (98.5%)	503 (99.0%)	247 (97.2%)
Treatment ongoing	77 (6.3%)	24 (2.9%)	19 (3.8%)	3 (1.2%)
Discontinued treatment	1145 (93.7%)	803 (97.1%)	484 (95.3%)	244 (96.1%)
Primary reason for discontinuation				
Adverse event (including death)	130 (10.6%)	77 (9.3%)	53 (10.4%)	26 (10.2%)
Patient withdrew consent	38 (3.1%)	38 (3.1%)	10 (2.0%)	7 (2.8%)
Progressive disease RECIST criteria	787 (64.4%)	577 (69.8%)	336 (66.1%)	153 (60.2%)
Clinical progression	108 (8.8%)	90 (10.9%)	61 (12.0%)	36 (14.2%
Physician's decision	60 (4.9%)	32 (3.9%)	18 (3.5%)	13 (5.1%)
Lost to follow-up	0	0	0	0
Other	22 (1.8%)	10 (1.2%	6 (1.2%)	9 (3.5%)
Died on study treatment or within 30 days of last treatment	57/1222 (4.7%)	34/827 (4.1%)	20/503 (4.0%)	19/147 (7.7%).

In addition to the safety data outlined above, the submission also included safety data the studies summarised below.

- Safety data on eribulin from 1136 subjects enrolled in 5 ongoing clinical studies not completed at the cut-off date for the submission: Phase Ib study of eribulin in combination

with carboplatin [104]; Phase II study of eribulin for soft-tissue sarcoma [207]; randomised Phase II study of neuropathy in breast cancer subjects comparing eribulin with ixabepilone [209]; Phase II study of eribulin for advanced breast cancer in Japan [221]; and Phase III study in advanced breast cancer comparing eribulin with capecitabine [301]. Safety data from the submitted progress reports from these 5 studies have been examined and are considered to be consistent with the pooled safety data from the AETP group.

- Safety data on eribulin from 9 Phase I and II studies in patients with solid tumours sponsored by the NCI (1 completed phase I study [NCI 5730] and 8 ongoing studies). None of these NCI studies involve the proposed indication. The submission included a safety summary for completed study 5730 (n=40), and progress reports for the other 8 NCI studies [7427 (n=16); 7444 (n=21); 7431 (n=70), 7435 (n=56), 7437 (n=41), 7448 (n=15), E805 (n=112), and S0168 (n=42)]. The safety data from these studies have been examined and are considered to be consistent with the pooled safety data from the AETP group.

  Comment: The safety database is considered to include an adequate number of patients for the assessment of eribulin at the proposed dose for the proposed indication. The major focus on the safety of eribulin in this evaluation clinical evaluation report is on the original comparative data from the pivotal study [305](eribulin versus TPC), supplemented by the safety data from the AETP group from the 11 Phase I/II/III studies. Patient disposition was similar in the AETP group, the BCP group, and the eribulin safety group from the pivotal study. This was not unexpected given the significant overlapping of patients among the three safety populations.

  In the pivotal study, the majority of randomised patients had discontinued treatment at the time of the cut-off date (484 [95.3%] and 244 [96.1%], eribulin and TPC groups, respectively). The primary reason for discontinuation in both treatment groups was progressive disease according to RECIST criteria, and the percentage of patients discontinuing for this reason was higher in the eribulin group than in the TPC group (336 [66.1%] and 153 [60.2%], respectively). Clinical progression not according to RECIST criteria resulted in 61 (12.0%) discontinuations in the eribulin group and 36 (14.2%) in the TPC group. In both the eribulin and the TPC groups, discontinuations due to adverse events occurred in a similar proportion of randomised patients (50 [9.8%] and 24 [9.4%], respectively).

8.2. Patient exposure

8.2.1. Pivotal Study [305]

Exposure to eribulin in the pivotal study is summarised below in Table 27. Of the 503 patients exposed to eribulin, 58.6% (n=295) received five or more treatment cycles [range 1, 23]. The median duration of exposure was 118 days [range 21, 497], the median dose intensity was 0.85 mg/m^2/week [range 0.2, 1.0], and the median relative dose intensity was 0.91 mg/m^2/week [range 0.3, 1.1]. There were 114 (22.7%) patients treated with eribulin for > 6 months and 12 (2.4%) patients treated for more than 1 year. Dose interruptions were required for 5.6% of patients (n=28), dose delays for 49.3% (n=248), and dose reductions for 28.8% (n=145).

Table 27: Study 305 – Exposure to eribulin; safety population.

Number of completed cycles (n, %)[a]	1-2 (81, 16.1%); 3-4 (127, 25,2%); 5- 6 (110, 21.9%); > 6 (185, 36.8%); range 1-23
Duration of exposure (days); n=503[b]	mean (sd) = 137.3 (92.64); median [range] = 118.0 (21, 497)
Dose intensity (mg/m^2/week); n=502[c, f]	mean (sd) = 0.78 (0.166); median [range] = 0.85 [0.2, 1.0]
Relative dose intensity; n=502[d, e, f]	mean (sd) = 0.84 (0.178); median [range] = 0.91 [0.3, 1.1]
Patients with dose interruption (n, %)	28 (5.6%)
Patients with dose delay (n, %)	248 (49.3%)
Patients with dose reduction	145 (28.8%)

a: Number of cycles = number of cycles patient received at least one dose of study drug.
b: Duration of treatment (exposure) = date of Day 1 of Final cycle + 21 - Date of First Dose.
c: Dose intensity (mg/m^2/week) = total dose per m2 received during study/(duration of treatment [exposure] in days/7).
d: Relative Dose intensity (mg/m^2/week) = (actual dose intensity [mg/m2])/ (Planned dose intensity [0.933 mg/m^2/week]).
e: There was one patient (17051012) for whom the actual administered dose was recorded incorrectly; this led to an incorrect calculation of the maximum relative dose intensity; but median data are not affected.
f: The body surface area was not recorded for one patient (20041003) therefore dose intensity and relative dose intensity data were not available.

In the pivotal study, nearly all of the 247 patients in the TPC group received chemotherapy (96.4%, n=238) with the remainder being treated with hormonal therapy (3.6%, n=9). The median duration of treatment in the chemotherapy group was 64.0 days [range: 1, 644]. Dose interruptions were required for 8.8% of patients (n=21), dose delays for 41.2% (n=98) and dose reductions for 26.5% (n=63).

> **Comment:** The median duration of exposure in the eribulin group (118.0 days) was longer than that in the TPC group treated with chemotherapy (64.0 days). Over half of the patients in the eribulin group received 5 or more cycles (58.6%) with a range of 1-23 cycles. Dose interruptions and dose reductions occurred with similar frequencies in the two treatment groups. However, dose delays were more common in patients in the eribulin group (49.3%) than in the TPC chemotherapy group (41.2%).

8.2.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

Exposure data for the AETP and BCP groups are provided in the submission. In both groups, more than 40% of patients were exposed to 5 or more cycles, and the median duration of exposure in the AETP group was 12.3 weeks [range 3, 153], and 15.1 weeks [range 3, 125] in the BCP group. The mean (sd) dose intensity was the same for both groups (0.85 [0.17]) as was the median relative dose intensity (0.92). Overall, the exposure data were similar for the AETP and BCP groups.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Overall Incidence

8.3.1.1.1. Pivotal Study [305]

In the pivotal study, AEs were defined as any untoward medical occurrence in a patient administered eribulin or TPC. All AEs, regardless of relationship to study drug or procedures, were collected beginning from the time the patient signed the study consent until the termination visit, but not during the follow-up period for disease progression and/or survival. AEs included any change in the patient's condition which included symptoms, physical findings or clinical syndromes.

AE severity was graded on the five-point scale according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3. Where a CTCAE grade did not exist for the AE,

the event was graded on a three-point scale (mild, moderate, severe). For a limited number of events, the Investigator graded the AE according to the three-point scale event even when CTCAE grading was available for that AE. The overall summary of treatment emergent adverse events (TEAEs) is provided below in Table 28.

Table 28: Study 305 – Treatment emergent adverse events; safety population.

Treatment emergent adverse events	Treatment Group						
			TPC group				
	Eribulin N=503 n (%)	TPC N=247 n (%)	Vinor-elbine N=61 n (%)	Gemcit-abine N=46 n (%)	Capec-itabine N=44 n (%)	Taxanes N=38 n (%)	Anthra-cyclines N=24 n (%)
Any AE	497 (98.8)	230 (93.1)	57 (93.4)	44 (95.7)	41 (93.2)	37 (97.4)	24 (100.0)
Any AE reported as treatment-related	474 (94.2)	192 (77.7)	49 (80.3)	35 (76.1)	35 (79.5)	33 (86.8)	23 (95.8)
Fatal SAEs and Other SAEs	126 (25.0)	64 (25.9)	16 (26.2)	12 (26.1)	13 (29.5)	8 (21.1)	7 (29.2)
SAE reported as treatment-related	59 (11.7)	17 (6.9)	5 (8.2)	2 (4.3)	4 (9.1)	2 (5.3)	2 (8.3)
Fatal SAEs	20 (4.0)	18 (7.3)	3 (4.9)	4 (8.7)	4 (9.1)	3 (7.9)	0 (0.0)
Other SAEs	114 (22.7)	56 (22.7)	14 (23.0)	10 (21.7)	11 (25.0)	7 (18.4)	7 (19.2)
AEs that Led to Dose Discontinuation	67 (13.3)	38 (15.4)	7 (11.5)	5 (10.9)	5 (11.4)	10 (26.3)	3 (12.5)
SAEs	20 (4.0)	20 (8.1)	5 (8.2)	3 (6.5)	2 (4.5)	7 (18.4)	1 (4.2)
Non-serious AEs	53 (10.5)	23 (9.3)	3 (4.9)	2 (4.3)	3 (6.8)	5 (13.2)	3 (12.5)
Other AEs of Interest							
AE that led to dose delay	177 (35.2)	80 (32.4)	27 (44.3)	18 (39.1)	10 (22.7)	14 (36.8)	5 (20.8)
AEs that led to dose interruption	25 (5.0)	25 (10.1)	7 (11.5)	5 (10.9)	10 (22.7)	2 (5.3)	1 (4.2)
AEs that led to dose reduction	85 (16.9)	39 (15.8)	12 (19.7)	7 (15.2)	8 (18.2)	6 (15.8)	5 (20.8)
AEs of CTCAE Grade 3	308 (61.2)	114 (46.2)	40 (65.6)	22 (47.8)	14 (31.8)	15 (39.5)	10 (41.7)
AEs of CTCAE Grade 4	148 (29.4)	33 (13.4)	12 (19.7)	7 (15.2)	1 (2.3)	6 (15.8)	2 (8.3)

Note: Treatment Emergent AE: Adverse events started on or after the date of administration of the first dose of study drug, or if they were present prior to the administration of the first dose of study drug and increased in severity during the study. Although a patient may have two or more adverse events, the patient is only counted once in each category. The same patient may appear in different categories. Percentages are based on the total number of patients in the treatment group. A fatal AE is defined as an outcome of FATAL or a Serious Criteria specified as DEATH.

Comment: In the pivotal study, almost all patients in the eribulin and TPC treatment groups experienced at least one AE (98.8%, n=497 and 93.1%, n=230, respectively). The major difference between the two treatment groups was the higher incidence in the eribulin group compared with the TPC group of CTCAE Grade 3 AEs (61.2%, n=308 and 46.2%, n=114, respectively), and CTCAE Grade 4 AEs (29.4%, n=148 and 13.4%, n=33, respectively). Fatal SAEs and other SAEs were experienced in a similar proportion of patients in both the eribulin and TPC treatment groups (25.0%, n=126 and 25.9%, n=64). AEs leading to dose discontinuation were similar between two treatment groups (13.3%, n=67 and 15.4%, n=38 eribulin and TPC, respectively), while AEs leading to dose delay, interruption or reduction were generally similar between the two groups. The comparison between eribulin and the five most commonly used drugs in the TPC group showed that the main difference related to the higher incidence of CTCAE Grade 3 AEs in the eribulin group compared with each of the five TPC drugs, apart from vinorelbine, and the higher incidence of CTCAE Grade 4 AEs in the eribulin group compared with each of the five TPC drugs.

8.3.1.1.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

Nearly all patients in both the AETP (1210, 99.0%) and the BCP (820, [99.2%]) groups experienced at least one TEAE. TEAEs leading to treatment discontinuation occurred in 13.7% (n=168) of patients in the AETP group, and 12.9% (n=101) in the BCP group. TEAEs leading to dose delays, interruptions, or reductions in the BCP group occurred with similar frequencies to those in the eribulin group in the pivotal study [305]. Data on the overall incidence of patients with TEAEs in the AETP and BCP groups is provided in the submission.

8.3.2. Most common AEs (irrespective of relationship to study treatment)

8.3.2.1. Pivotal Study [305]

Data on TEAEs reported with an incidence of 10% or more in the eribulin and the TPC groups are provided in the CSR.

The most frequently reported AEs (≥ 20%) in patients in either treatment group (eribulin vs TPC) were: asthenia/fatigue (53.7% vs 39.7%); neutropenia (51.7% vs 29.6%); alopecia (44.5% vs 9.7%); peripheral neuropathy (34.6% vs 16.2%); nausea (34.6% vs 28.3%); constipation (24.7% vs 20.6%); leukopenia (23.1% vs 11.3%); arthralgia/myalgia (21.7% vs 11.7%); weight decreased (21.3% vs 14.2%); pyrexia (20.9% vs 12.6%); and anaemia (18.7% vs 22.7%).

The majority of common AEs were CTCAE Grade 1 or 2. There were four CTCAE Grade 3 AEs reported with an incidence of ≥ 5% with eribulin (vs TPC): neutropenia (21.1% vs 14.2%); leukopenia (11.7% vs 4.9%); asthenia/fatigue (8.2% vs 10.1%); and peripheral neuropathy (7.8% vs 2.0%). There was one Grade 4 AEs reported with an incidence of ≥ 5% with eribulin (vs TPC): neutropenia (24.1% vs 6.9%).

In addition to the AEs reported with an incidence of ≥ 20% in either treatment group summarised above, the following AEs occurred with an incidence of ≥ 10% in the eribulin group (vs TPC): anorexia (19.5%, n=98 vs 13.0%, n=32); headache (19.3%, n=97 vs 11.7%, n=29); diarrhoea (18.3%, n=92 vs 18.2%, n=45); vomiting (18.1%, n=92 vs 17.8%, n=44); dyspnoea (15.7%, n=79 vs 12.6%, n=31); back pain (15.7%, n=79 vs 7.3%, n=18); arthralgia 13.7%, n=69 vs 5.3%, n=13); peripheral sensory neuropathy (12.3%, n=62 vs 4.0%, n=10); pain in extremity (11.3%, n=57 vs 10.1%, n=25); bone pain (11.9%, n=60 vs 9.3%, n=23); parasthesia (11.1%, n=56 vs 6.5%, n=16); and myalgia (10.7%, n=54 vs 6.9%, n=17).

Also of note was the higher incidence of psychiatric disorders in the eribulin group (19.1%, n=96) compared with the TPC group (11.7%, n=29). The main difference between the two groups consisted primarily of the higher incidence in the eribulin group compared with TPC group of insomnia (7.6%, n=38 vs 4.0%, n=10), anxiety (5.4%, n=27 vs 4.5%, n=11), and depression (5.0%, n=25 vs 1.2%, n=11). However, the observed difference in psychiatric disorders between the two groups might reflect (at least partially) the difference in baseline incidence of patients with pre-existing significant psychiatric conditions (17.3%, n=88 and 13.8%, n=35, eribulin and TPC, respectively). Furthermore, the incidence of patients with baseline symptoms of psychiatric disorders was higher in the eribulin group (16.5%, n=84) than in the TPC group (13.0%, n=33), and the major difference between the two treatment groups was the higher incidence of both insomnia and depression in the eribulin group. Data were provided on treatment-emergent psychiatric disorders (irrespective of relationship to treatment) in the pivotal study [305].

The AEs (all Grades) reported with an incidence of ≥ 10% with eribulin and more frequently than each of the five most commonly used chemotherapy agents in the TPC group (*post hoc* subgroup analyses) were: *asthenia/fatigue 53.7%* (vs 50.8% vinorelbine; 44.7% taxanes; 38.6% capecitabine; 37.0% gemcitabine; 33.3% anthracyclines); *neutropenia 51.7%* (vs 49.2% vinorelbine; 37.0% gemcitabine; 39.5% taxanes; 20.8% anthracyclines; 4.5% capecitabine); *alopecia 44.5%* (vs 34.2% taxanes; 6.8% capecitabine; 6.5% gemcitabine; 4.5% anthracycline; 3.3% vinorelbine); *leukopenia 23.1%* (vs 18.4% taxanes; 17.4% gemcitabine; 16.4% vinorelbine; 2.3% capecitabine; 0% anthracyclines); *weight decreased 21.3%* (vs 18.4% taxanes; 16.4% vinorelbine; 13.6% capecitabine; 12.5% anthracyclines; 10.9% gemcitabine); *anorexia 19.5%* (vs 18.0% vinorelbine; 15.8% taxanes; 13.6% capecitabine; 13.0% gemcitabine; 12.5% anthracyclines); *headache 19.3%* (vs 18.2% capecitabine; 14.8% vinorelbine; 13.0% gemcitabine; 10.5% taxanes; 8.3% anthracyclines); and *back pain 15.7%* (vs 11.5% vinorelbine; 9.1% capecitabine; 5.3% taxanes; 4.3% gemcitabine; 0% anthracyclines).

> **Comment:** In the pivotal study, the reported CTCAE Grade 3 and 4 TEAEs of main concern with eribulin treatment were neutropenia, leukopenia, and peripheral neuropathy. The

most commonly reported TEAEs (all Grades) of concern with eribulin treatment were asthenia/fatigue, neutropenia, alopecia, peripheral neuropathy, nausea, constipation and leukopenia. In a post hoc subgroup analysis, TEAEs (all Grades) occurring with an incidence of ≥ 10% with eribulin and more frequently with eribulin compared with each of the five most commonly used chemotherapy drugs in the TPC group were asthenia/fatigue, neutropenia, leukopenia, weight decreased, anorexia, headache and back pain.

8.3.2.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

The most common TEAEs in the AETP and BCP groups were consistent with those in the pivotal study. The most commonly reported TEAEs (AETP vs BCP) were: asthenia/fatigue (60.2% vs 59.9%); neutropenia (53.5% vs 55.3%); alopecia (43.8% vs 50.4%); peripheral neuropathy (40.7% vs 41.5%); and nausea (39.2% vs 39.8%). Data on the most common TEAEs occurring in ≥ 10% of all eribulin treated patients are provided in the CSR.

CTCAE Grade 3+4 TEAEs (any) were reported in 66.8% (n=816) of patients in the AETP group, and 68.1% (n=563) of patients in the BCP group. The most commonly reported CTCAE Grade 3+4 TEAEs (AETP vs BCP) occurring in ≥ 10% of patients in either group were: neutropenia (46.2%, n=564 vs 48.9%), n=404; leukopenia (12.8%, n=157 vs 14.1%, n=116); and asthenia/fatigue (10.8%, n=132 vs 10.4%, n=86).

8.3.3. Treatment-related adverse events (adverse drug reactions)

8.3.3.1. Pivotal Study [305]

Treatment-related AEs (investigator reported) occurred in 94.2% (n=474) of eribulin treated patients, with the percentage of patients experiencing CTCAE Grade (G) toxicities being: 13.9%, n=70 (G1); 22.5%, n=113 (G2); 30.0%, n=151 (G3); 26.2%, n=132 (G4); and 1.0%, n=5 (G5). Data on TEAEs reported with a frequency of ≥ 5% in the eribulin group are provided in the dossier.

Treatment related AEs (investigator reported) occurred in 77.7% (n=129) of TPC treated patients, with the percentage of patients experiencing CTCAE Grade (G) toxicities being: 11.7%, n=29 (GI); 28.3%, n=70 (G2); 28.7%, n=71 (G3); 6.9%, n=17 (G4); and 0.8%, n=2 (G5). TEAEs reported with a frequency of ≥ 5% in the TPC group are provided in the dossier.

The most commonly related AEs reported as treatment related by the investigators and occurring in ≥ 20% of patients in either treatment group were (eribulin vs TPC): neutropenia 50.7% (n=255) vs 27.5% (n=68); asthenia/fatigue 45.5% (n=229) vs 29.6% (n=73); alopecia 44.1% (n=221) vs 9.3% (n=23); peripheral neuropathy 31.6% (n=159) vs 13.8% (n=34); nausea 29.8% (n=150) vs 23.1% (n=57); and leukopenia 22.7% (n=114) vs 10.9% (n=27).

8.3.3.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

Treatment-related AEs were reported in 93.9% (n=1148) of patients in the AETP group, with the percentage of patients experiencing CTCAE Grade (G) toxicities being: 12.2%, n=149 (G1); 22.6%, n=226 (G2); 31.0%, n=379 (G3); 27.6%, n=337 (G4); and 0.6%, n=7 (G5). Treatment-related AEs were reported in 95.5% (n=790) of patients in the BCP group, with the percentage of patients experiencing CTCAE Grade (G) toxicities being: 12.0%, n=99 (G1), 22.4%, n=185 (G2); 30.8%, n=255 (G3); 29.6%, n=245 (G4); and 0.7%, n=6 (G5).

Treatment related AEs occurring in ≥ 20% of patients in either the AETP group or BCP group, respectively, were: neutropenia 52.5% (n=642) vs 54.5% (n=451); asthenia/fatigue 51.9% (n=634) vs 52.8% (n=437); alopecia 42.3% (n=517) vs 49.7% (n=411); nausea 33.6% (n=411) vs 35.1%, (n=290); peripheral neuropathy 29.4% (n=359) vs 32.0% (n=265); anaemia 22.4% (n=274) vs 20.3% (n=168); and leukopenia 20.9% (n=255) vs 22.1% (n=183).

Comment: The treatment-related AE profiles were similar in both the AETP and BCP groups. In addition, the treatment-related AE profiles were similar in the AETP group, BCP group, and the eribulin safety group from the pivotal study [305].

8.3.4. Deaths and other serious adverse events

8.3.4.1. Deaths

8.3.4.1.1. Pivotal study [305]

As the primary endpoint in the pivotal study was OS in women with heavily pre-treated advanced metastatic breast cancer, many deaths were expected and were reported. In the safety population, at the original data cut-off date (12 May 2009), 271 (53.9%) patients in the eribulin group and 143 (57.9%) patients in the TPC group had died (see Table 29, below). In both treatment groups, the primary reason for death was progressive disease (50.5% [n=254] and 54.7% [n=135], eribulin and TPC, respectively). In the pivotal study, there were 20 (4.0%) patients in the eribulin group and 19 (7.7%) patients in the TPC group who died during study treatment or within 30 days of their last study treatment.

Table 29: Study 305 – Summary of deaths; safety population.

	Treatment Group	
	Eribulin N=503 n (%)	TPC N=247 n (%)
Subject Status		
Dead	271 (53.9)	143 (57.9)
Alive	232 (46.1)	104 (42.1)
Cause of Death		
Toxicity	1 (0.2)[a]	0 (0.0)
Progressive Disease	254 (50.5)	135 (54.7)
Other	16 (3.2)	8 (3.2)

a: Patient 20081018 was recorded as death due to toxicity on Day 287, but no AE leading to death was reported. The last dose of eribulin had been administered on Day 49.

In the 20 patients treated with eribulin who died within 30 days of last study treatment or during study treatment there were 9 patients in whom death was reported as being due to a fatal SAE: febrile neutropenia (reported as treatment related); diabetic ketoacidosis; lung infection (reported as treatment related); pulmonary embolism; respiratory failure; dyspnoea; bronchopneumonia (reported as treatment related), sepsis, and dyspnoea (reported as treatment related). In the remaining 11 of the 20 patients, the cause of death was investigator reported to be due to progressive disease and fatal SAEs were reported in 8 of these patients. There were 10 patients with SAEs leading to death more than 30 days after the last dose of eribulin in whom death was reported to be associated with fatal SAEs. The listing of deaths in eribulin treated patients associated with an AE, and deaths that occurred within 30 days of the last study treatment in the safety population are summarised in the dossier.

In the 19 patients treated with eribulin who died within 30 days of last study treatment or during study treatment there were 6 patients in whom death was reported as being due to a fatal SAE: pulmonary embolism; aspergillosis (reported as treatment related); pneumonia, respiratory failure; asthenia; and embolism. In the remaining 13 of the 19 patients, the cause of death was reported to be due to progressive disease, and fatal SAEs were reported in 11 of these patients. There were 2 patients with SAEs leading to death more than 30 days after the last dose of eribulin in whom death was reported to be associated with a fatal SAE. The listing of deaths in TPC treated patients associated with an AE and deaths that occurred within 30 days of the last study treatment in the safety population are summarised in the dossier.

Comment: In the pivotal study, deaths occurring during study treatment or within 30 days of the last dose due to SAEs occurred less frequently in eribulin treated patients

(4.0% [n=20]) than in TPC treated patients (7.7% [n=18]). Similarly, AEs with an outcome of death also occurred less frequently in the eribulin group (4.0%) than in the TPC group (7.3%). The causes of death were mostly related to disease progression and were not unexpected given the patient population.

Fatal SAEs leading to death within 30 days of the last dose and reported as being treatment related occurred in 5 (1.0%) patients in the eribulin group and 2 (0.8%) patients in the TPC group. The fatal treatment related SAEs in the eribulin group were: febrile neutropenia (56 year old white female; 36 days on treatment; 7 days since last dose); lung infection (52 year old white female; 51 days on treatment; 11 days since last dose); bronchopneumonia (55 year old white female; 22 days on treatment; 12 days since last dose); dyspnoea (53 year old white female; 8 days on treatment; 12 days since last dose); dyspnoea (60 year old white female with cause of death progressive disease; 8 days on treatment; 15 days since last dose). The fatal treatment related SAEs in the TPC group were: aspergillosis (73 year old white female; 127 days on treatment; 15 days since last dose); febrile neutropenia (43 year old white female with cause of death progressive disease; 45 days on treatment; 3 days since last dose).

8.3.4.1.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

In the AETP and BCP groups there were a total of 68 (5.6%) and 39 (4.7%) deaths, respectively, occurring within 30 days of the of the last dose or within 30 days of the last study termination visit, whichever was the longest. Of these deaths, 10 (0.8%) and 6 (0.7%), respectively, were considered treatment-related.

8.3.4.2. Other Serious Adverse Events

8.3.4.2.1. Pivotal Study [305]

An AE was considered serious if it resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect. The definition of SAEs is consistent with ICH E6 GCP guidelines. Serious adverse events, regardless of causality assessment, were collected through to the termination visit and for 30 days following study drug discontinuation, whichever was longer. Treatment-emergent SAEs (fatal and others) were reported in 126 (25.0%) patients in the eribulin group and 64 (25.9%) patients in the TPC group.

In the eribulin and the TPC groups, the respective number of patients in which SAEs were reported as treatment related were 59 (11.7%) and 17 (6.9%), fatal 20 (4.0%) and 18 (7.3%), and other 114 (22.7%) and 56 (22.7%). The most commonly reported treatment-emergent SAEs (≥ 1% of patients in either treatment group), including those considered to be treatment related are summarised below in Table 30.

Table 30: Study 305 – Treatment-emergent SAEs (n [%]) reported for at least ≥ 1% of patients in either group, including those considered to be treatments; safety population.

Preferred Term	Eribulin (n=503)	TPC (n=247)	Treatment-Related
Febrile Neutropenia	21 (4.2)	3 (1.2)	21 (4.2) vs 1 (0.4)
Neutropenia	9 (1.8)	0 (0.0)	9 (1.8) vs 0
Nausea	7 (1.4)	2 (0.8)	-
Asthenia/fatigue	7 (1.4)	6 (2.4)	3 (0.6) vs 4 (1.6)

Preferred Term	Eribulin (n=503)	TPC (n=247)	Treatment-Related
Pyrexia	7 (1.4)	2 (0.8)	5 (1.0) vs 1 (0.4)
Hypercalcaemia	7 (1.4)	2 (0.8)	-
Dyspnoea	7 (1.4)	9 (3.6)	-
Pulmonary Embolism	7 (1.4)	3 (1.2)	-
General Physical Health Deterioration	6 (1.2)	2 (0.8)	-
Pleural Effusion	6 (1.2)	4 (1.6)	-
Vomiting	5 (1.0)	1 (0.4)	-
Malignant neoplasm progression	5 (1.0)	2 (0.8)	-
Back Pain	3 (0.6)	3 (1.2)	-
Abdominal Pain	1 (0.2)	3 (1.2)	-
Diarrhoea	0 (0.0)	4 (1.6)	0 vs 3 (1.2)
Performance Status Decreased	0 (0.0)	3 (1.2)	-

a: Although a patient could have two or more SAES within each row, the patient was only counted once in each row. The same patient could appear in multiple categories.

Comment: In the pivotal study, the most common treatment-emergent SAEs in the eribulin group (vs TPC) was febrile neutropenia 4.2% (n=21) vs 1.2% (n=3). Apart from febrile neutropaenia in the eribulin group, no other SAEs in either treatment group occurred in ≥ 2% of patients. Other SAEs reported in ≥ 1% of patients in either treatment group and with a greater incidence in the eribulin group compared with the TPC group were neutropenia, nausea, vomiting, pyrexia, general physical health deterioration, hypercalaemia, pulmonary embolism, and malignant neoplasm progression. The only treatment-emergent SAEs occurring with a frequency of ≥ 1% in the eribulin group compared with the TPC group were febrile neutropenia and neutropenia.

8.3.4.2.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

Treatment-emergent SAEs (any) irrespective of relationship to treatment were reported in 29.3% (n=358) of patients in the AETP group, and 27.1% (n=224) of patients in the BCP group. Treatment related (possibly + probably) SAEs (any) were reported in 12.5% (n=152) and 12.3% (n=101) of patients in the AETP and BCP groups, respectively. The most commonly reported SAEs in the AETP and BCP groups were consistent with those in the eribulin group in the pivotal study [305].

8.4. Discontinuation due to adverse events

8.4.1. Pivotal Study [305]

Treatment emergent AEs reported in ≥ 1% of patients in either group are summarised below in Table 31. Blood and lymphatic system disorders leading to discontinuation (eribulin vs TPC) and were anaemia (0.2%, n=1 vs 0.8%, n=2), and pancytopenia (0.2%, n=1 vs 0%).

Table 31: Study 305 – Treatment-emergent AEs, n (%) in ≥ 1% of patients in either group; safety population.

MedDRA Preferred Terma	Eribulin (n=503)	TPC (n=247)
Any AE	67 (13.3)	38 (15.4)
Peripheral neuropathy b	24 (4.8)	3 (1.2)
Asthenia/fatigue	9 (1.8)	4 (1.6)
Ascites	2 (0.4)	3 (1.2)
Dyspnoea	1 (0.2)	3 (1.2)
Palmar plantar erythrodysaesthesia	0 (0.0)	4 (1.6)

a: Although a patient could have two or more SAES within each row, the patient was only counted once in each row. The same patient could appear in multiple categories. b: Peripheral neuropathy includes: peripheral neuropathy, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and parasthesia.

Comment: In the pivotal study, there 67 (13.3%) patients in the eribulin group and 38 (15.4%) patients in the TPC group who discontinued because of AEs. The most common AE resulting in discontinuation in the eribulin group was peripheral neuropathy (4.8% vs 1.2%, eribulin and TPC, respectively). Discontinuations due to blood disorders occurred in < 1% of patients in both treatment groups (0.8%, n=4 and 0.8%, n=2, eribulin and TPC, respectively). TEAE haematology events leading to discontinuation (eribulin vs TPC) were: neutropenia 0.6% (n=3) vs 0 (0%); thrombocytopenia 0.2% (n=1) vs 0.8% (n=2); anaemia 0.2% (n=1) vs 0 (0%); and leukopenia 0 (0%) vs 0.4% (n=1).

8.4.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

Treatment-emergent AEs leading to discontinuation were reported in 13.7% (n=168) of patients in the AETP group and 12.9% (n=107) of patients in the BCP group. In the AETP group, of the 168 patients discontinuing treatment, 71 were considered not related to treatment and 97 were considered related to treatment. In the BCP group, of the 107 patients discontinuing treatment, 41 were considered not related to treatment and 66 were considered related to treatment. The SAE profiles were similar in the AETP group, the BCP group, and the eribulin treated safety population group in pivotal study [305].

8.5. Adverse events of special interest

8.5.1. Pivotal Study [305]

The pivotal study [305] included a summary of AEs of special interest (by CTCAE grade) that are commonly seen with cytotoxic chemotherapy. These AEs were asthenia/fatigue, alopecia, febrile neutropenia, neutropenia, and peripheral neuropathy (consisting of peripheral neuropathy, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy,

peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and parasthesia). The results are summarised below in Table 32.

Table 32: Study 305 – AEs of special interest by CTCAE grade; safety population.

Combined name, preferred terms included[a, b]	Treatment Group											
	Eribulin N=503 n (%)						TPC N=247 n (%)					
	Total[c]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total[c]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asthenia /fatigue	270 (53.7)	102 (20.3)	111 (22.1)	41 (8.2)	3 (0.6)	0 (0.0)	98 (39.7)	29 (11.7)	36 (14.6)	25 (10.1)	0 (0.0)	1 (0.4)
Neutropenia	260 (51.7)	5 (1.0)	27 (5.4)	106 (21.1)	121 (24.1)	0 (0.0)	73 (29.6)	5 (2.0)	16 (6.5)	35 (14.2)	17 (6.9)	0 (0.0)
Alopecia	224 (44.5)	132 (26.2)	87 (17.3)	-	-	-	24 (9.7)	11 (4.5)	11 (4.5)	-	-	-
Peripheral neuropathy[d]	174 (34.6)	79 (15.7)	48 (9.5)	39 (7.8)	2 (0.4)	0 (0.0)	40 (16.2)	19 (7.7)	14 (5.7)	5 (2.0)	0 (0.0)	0 (0.0)
Arthralgia/ myalgia	109 (21.7)	66 (13.1)	35 (7.0)	2 (0.4)	0 (0.0)	0 (0.0)	29 (11.7)	17 (6.9)	4 (1.6)	3 (1.2)	0 (0.0)	0 (0.0)
Febrile Neutropenia	23 (4.6)	-	-	15 (3.0)	6 (1.2)	1 (0.2)	4 (1.6)	-	-	2 (0.8)	1 (0.4)	1 (0.4)

a: Although a patient may have two or more adverse events within each row, the patient is only counted once in each row. The same patient may appear in multiple categories.
b: If a patient had the same adverse event with more than one CTCAE grade, the highest CTCAE grade was used. If the CTCAE grade is missing, severity was used.
c: The number of patients by CTCAE grade may not equal the number with the individual AE since a small proportion of events was reported as mild, moderate or severe, rather than by CTCAE grade.
d: Peripheral neuropathy includes: peripheral neuropathy, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and parasthesia.

Neuropathy

Peripheral neuropathy was reported in 34.6% (n=174) of patients who received eribulin, and at Grade 3 and Grade 4 levels in 39 (7.8%) and 2 (0.4%) patients, respectively. Discontinuations due to neuropathy occurred in 4.8% (n=27) of eribulin treated patients, indicating that treatment was able to continue in 84.4% (n=147) of patients who developed neuropathy. Of the patients with Grade 3/4 peripheral neuropathy, 63% (15/41) were able to continue treatment with eribulin. Overall, in 43 (8.5%) patients with peripheral neuropathy treatment was discontinued or dose was delayed discontinued or reduced.

Time to development or progression of Grade 2 or higher peripheral neuropathy was estimated using Kaplan-Meier methods. This was measured as the time interval from first dose to first recorded peripheral neuropathy of Grade 2 or higher in patients with no baseline peripheral neuropathy or baseline Grade 1, and the time from first dose to first recorded peripheral neuropathy Grade 3 or higher in patients with a baseline of Grade 2. Baseline Grade was assessed using signs, symptoms and medical history. Patients with peripheral neuropathy (ongoing) recorded in their medical history without a reported CTCAE grade were assigned a baseline score of Grade 1 or 2. Patients were censored at death, loss to follow-up, or the data cut-off date if they had not developed peripheral neuropathy or had progression of peripheral neuropathy.

In 84/440 (19.1%) patients in the eribulin group (no baseline peripheral neuropathy/Grade 1 if baseline information missing) peripheral neuropathy developed or progressed during treatment to Grade 2 or above compared with 18/214 (8.4%) of patients in the TPC group: HR = 2.309 [95% CI: 1.388, 3.841]. Kaplan-Meier estimates of the 1-year development/progression rate indicated that eribulin treated patients had a greater chance of development/progression of peripheral neuropathy within the first year compared with TPC treated patients (21.4% and 9.5%, eribulin and TPC, respectively). The 2-year Kaplan-Meier estimates were 23.1% and 9.5%, eribulin and TPC, respectively.

> **Comment:** The most frequently reported AE of special interest in the eribulin treated group was asthenia fatigue (53.7%, n=270), and most of the reports were Grade 1 or 2 toxicities. Neutropenia was the second most frequently reported AE of special interest in

the eribulin group (51.7%, n=260), and the majority of reports were Grade 3 and 4 toxicities (G3 + G4 = 45.1% [n=227]). Febrile neutropenia (4.6%, n=23) occurred less frequently than neutropenia, but all events were reported as Grade 3, 4, or 5 toxicities. Alopecia occurred in 44.5% (n=224) of patients, and all reports were Grade 1 (partial) or 2 (complete) as this AE does not include ≥ Grade 3 events. Arthralgia also occurred commonly (21.7%, n=109), and most of the reports were Grade 1 and 2 toxicities.

Peripheral neuropathy occurred commonly (34.6%, n=174), and most of the reports were Grade 1 or 2 toxicities. Time-to-event analysis estimated that the risk of neuropathy developing or progressing to Grade 2 or above during treatment was 2.3-fold higher in the eribulin group than in the TPC group in patients without peripheral neuropathy at baseline or Grade 1 set for those with missing baseline data. The sponsor states that the results for the comparison between eribulin and TPC for the time-to-event analysis "do not take into account that many of the TPC treatments are not associated with the development of peripheral neuropathy. Of the TPC groups, only patients receiving vinorelbine, capecitabine or taxanes experienced development/progression of peripheral neuropathy. Amongst these, the frequency of development/progression of peripheral neuropathy was highest in the taxanes group".

The time-to-event analyses for the taxane, vinorelbine, and capecitabine groups for development/progression of neuropathy to Grade 2 or above in which missing baseline data had been set to Grade 1 were: taxane group - 14/71 (19.7%) eribulin vs 9/38 (23.7%) taxane (HR = 0.790 [95% CI: 0.342, 1.826]); vinorelbine group - 20/118 (16.9%) eribulin vs 5/62 (8.1%) vinorelbine ([HR = 2.176 [95% CI: 0.816, 5.797]); and capecitabine group - 16/77 (20.8%) eribulin vs 4/44 (9.1%) capecitabine (HR = 2.434 [95% CI: 0.813, 7.292]). Time-to event analyses in the gemcitabine and anthracyclines groups were not evaluable due to no observed events in the TPC groups.

Of the 39 patients who developed Grade 3 peripheral neuropathy, 13 had pre-existing peripheral neuropathy at baseline. However, the 2 patients who developed Grade 4 peripheral neuropathy had no peripheral neuropathy at baseline. Worsened neuropathy (i.e., a neuropathy AE with a CTCAE Grade higher than baseline), was reported in 29.1% of patients with pre-existing Grade 1 (n=87) or Grade 2 (n=16) neuropathy. In comparison, 32.9% of the 38 patients without neuropathy prior to eribulin treatment experienced a neuropathy AE. Grade 3 and 4 neuropathy was experienced by 12.6% and 0%, respectively, of patients with pre-existing neuropathy, and by 7.0% and 0.5%, respectively, of patients without pre-existing neuropathy.

8.5.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

8.5.2.1. Neuropathy

Peripheral neuropathy based on the broad MedDRA SMQ was reported for 497 (40.7%) and 343 (41.5%) patients in the AETP and the BCP groups, respectively. The broad list of peripheral neuropathy terms included the broad SMQ of preferred terms for peripheral neuropathy supplemented to include hyperesthesia, painful response to stimuli, pallanesthesia, and allodynia.

Kaplan-Meier estimates of time-to-onset of treatment-emergent peripheral neuropathy showed a progressive increase in events over time. The sponsor considered these results to be consistent with the observation that patients on therapy for greater than 6 months or with a cumulative eribulin dose of greater than 11.2 mg/m^2 had a higher incidence of neuropathy. The Kaplan-Meier estimate of median time-to-onset of any treatment-emergent peripheral neuropathy was 22.7 weeks in the AETP group and 23.4 weeks in the BCP group. The incidence of any treatment emergent peripheral neuropathy was 32.7% (400/1222) in the AETP group and 34.8% (288/827) in the BCP group.

Of the 400 patients in the AETP group with treatment emergent peripheral neuropathy (any), resolution of the event was reported in 50 (12.5%) patients with a median time to resolution of

8.1 weeks. Of the 288 patients in the BCP group with treatment emergent peripheral neuropathy (any), resolution of the event was reported in 41(14.2%) patients with a median time to resolution of 8.1 weeks. The sponsor considered that interpretation of these analyses "is limited as patient follow-up after the last treatment may only have been at the time of the study termination visit (which occurred ≤30 days after their last treatment). Furthermore, subsequent anticancer therapy was often initiated before the event of neuropathy had fully resolved. As a consequence, time to resolution in > 80% of patients was censored, precluding the ability to draw firm conclusions regarding the time to resolution of neuropathy" (i.e., censoring was observed in 83.3% (250/300) of patients in AETP group and 80.8% (172/213) of patients in BCP group). The results of the updated analyses in the sponsor's response to the EMEA's 120 day questions are consistent with those seen in the original analyses.

In a sub-group analysis in the BCP group, the incidence of treatment related neuropathy was similar in patients without pre-existing neuropathy, with Grade 1 pre-existing neuropathy, and with Grade ≥ 2 pre-existing neuropathy (31.5% [197/625], 34.5% [49/142], and 29.6% [8/27], respectively). In a sub-group analysis of patients with diabetes mellitus there was no significant difference in the incidence of treatment related peripheral neuropathy in patients with and without diabetes mellitus in both the AETP and BCP groups.

8.5.2.2. Neutropenia

Neutropenia was reported in 53.3% (n=651) and 55.3% (n=457) patients in the AETP and BCP groups, respectively, and the corresponding figures for febrile neutropenia were 4.7% (n=57) and 4.7% (n=39). In both groups, the most commonly reported serious TEAE was febrile neutropenia (3.8%, n=47, [AETP] and 3.9%, n=32, [BCP]). Neutropenia was reported as a serious TEAE in 1.7% (n=21) and 1.9% (n=16) of patients in the AETP and BCP groups, respectively. Neutropenic sepsis was reported in 0.4% (n=5) and 0.2% (n=2) of patients in the AETP and BCP groups, respectively, and all events were considered treatment-related by the investigator. Neutropenic sepsis was Grade 3/4 in 0.3% (n=3) and 0.2% (n=2) of patients in the AETP and BCP groups, respectively subjects, respectively.

8.5.2.3. Other events

Fatigue was reported in 39.0% (n=476) and 33.0% (n=273) of patients in the AETP and the BCP groups respectively. *Asthenia* was reported in 25.0% (n=305) and 29.9% (n=247) of patients in each group, respectively. The combined terms (fatigue and asthenia) were reported in 60.2% (n=736) and 59.9% (n=736) of patients in each population, respectively. The numbers of patients for each term do not add up to the total for the combined terms because of cases where the same subject was reported with both events, and therefore counted only once in the combination.

Nausea was reported in 39.2% (n=479) and 39.8% (n=329) of patients in the AETP and the BCP groups, respectively. However, premedication with anti-emetic medication prior to eribulin administration was not a requirement in any of the pooled studies. *Alopecia* was reported in 43.8% (n=535) and 50.4% (n=417) of patients in the AETP and the BCP groups, respectively.

8.6. Laboratory tests

Laboratory test data were provided for clinical chemistry, haematology and urinalysis. Urinalysis data from the pivotal study [305] were not available, although the CSR indicated that dipstick analysis and microscopic analysis (if clinically indicated) were to be undertaken. Clinical laboratory testing was performed at the clinical site or associated laboratory. The results for laboratory test data included: summaries of mean clinical chemistry and haematology values at each visit, including mean changes from baseline; summaries of selected laboratory tests by CTCAE grade and abnormal laboratory tests by CTCAE grade for clinical chemistry; summaries of selected laboratory tests by CTCAE grade for haematology; shift tables

of haematology values by normal range and by CTCAE grade; shift tables for clinical chemistry values by normal range and by CTCAE grade; shift tables for abnormal clinical chemistry and haematology values by CTCAE; and number and percentage of patients who experienced treatment-emergent abnormal laboratory values (TEAVs) at any post-baseline (TEAVs were defined as values which changed by at least 2 CTCAE grades from normal or Grade 1 at baseline).

8.6.1. Liver function

8.6.1.1. Pivotal Study [305]

Liver function laboratory data were assessed for evidence of drug induced liver injury (DLI) using ALT/AST levels and total bilirubin levels (TBL) which were consistent with Hy's Law criteria (i.e., simultaneous occurrence of ALT/AST levels ≥ 3 x ULN and TBL ≥ 2, in the absence of another cause). In the eribulin group, there were 8 (1.6%) patients who experienced concurrent TBL ≥ 2 x ULN and AST/ALT levels > 3 x ULN compared with 4 (1.6%) patients in the TPC group. However, review of the medical history of the 12 patients in the study with concurrent TBL ≥ 2 x ULN and AST/ALT levels ≥ 3 x ULN showed that none of the patients can be considered to meet Hy's Law criteria for DLI due to other reasons being present to account for the findings. Examination of the data listings showed that the ALT/AST and total TBL abnormalities could be accounted for by liver metastases in 7 of the 8 eribulin treated patients, and all 4 of the TPC treated patients. The remaining eribulin treated patient without liver metastases had a maximum bilirubin level of 46.2 µmol/L at an unscheduled visit during the treatment period and levels returned to the normal range prior to the next visit and during subsequent cycles of treatment.

In the eribulin group, total bilirubin levels (TBLs) ≥ 2 x ULN were reported at least once in 3% (n=15) of patients compared with 4.5% (n=11) of patients in the TPC group. In the eribulin group, ALT levels ≥ 3 x ULN were reported in 16.5% (n=83) at least once compared with 8.9% (n=22) of patients in the TPC group. In the eribulin group, AST levels ≥ 3 x ULN were reported at least once in 17.5% (n=88) of patients compared with 11.8% (n=29) of patients in the TPC group. In the eribulin group, there were 9 (1.8%) patients with an ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN reported at least once compared with 6 (2.4%) patients in the eribulin group.

8.6.1.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

There were no marked differences between the AETP and BCP groups in the incidence of treatment-emergent liver function abnormalities (TEAVs) (see Table 33, below). TEAVs were defined as values which changed by at least 2 CTCAE grades from normal or Grade 1 at baseline.

Table 33: Treatment-emergent abnormal LFT values (TEAVs); safety population.

	AETP	BCP
ALT	2.7% (33/1218)	3.4% (28/826)
AST	3.9% (47/1218)	4.5% (37/826)
TBL increased	1.2% (15/1218)	1.1 % (9/826)
SAP	4.0% (48/1212)	4.4% (36/825)

TEAVs were defined as values which changed by at least 2 CTCAE grades from normal or Grade 1 at baseline.

The ALT shift table for CTC Grade from baseline to post-baseline in the BCP group is summarised below in Table 34. The highest proportion of patients in the BCP group shifted from Grade 0 at baseline to Grade 1 post-baseline (28.7%). Shifts in ALT from baseline 0 to post-baseline Grade ≥ 3 were uncommon (0.5%). During the entire treatment period, 346 (42.1%) and 119 (14.5%) of patients in the BCP group had worst ALT of CTCAE Grade 1 and Grade 2, respectively. In the BCP group, the shift table for ALT was consistent with the shift table for AST, and the highest proportion of AST shifts were from baseline Grade 0 to post-baseline Grade 1 (31.4% of patients). In addition, the shift tables for ALT and AST in the BCP group were consistent with those in the AETP group.

Table 34: ALT shift table from baseline to post-baseline in eribulin treated patients in the BCP group, n (%).

Post-Baseline	BCP – Baseline CTC Grade					
CTCAE Grade	0	1	2	3	4	Total
Grade 0	315 (38.3)	12 (1.5)	0	0	0	327 (39.8)
Grade 1	236 (28.7)	100 (12.2)	9 (1.1)	1 (0.1)	0	346 (42.1)
Grade 2	55 (6.7)	51 (6.2)	13 (1.6)	0	0	119 (14.5)
Grade 3	4 (0.5)	16 (1.9)	8 (1.0)	2 (0.2)	0	20 (3.6)
Grade 4	0	0	0	0	0	0

Note: The percentages are based on the number of subjects who started the baseline and the relevant cycle in the integrated analysis set.

8.6.2. Kidney function

8.6.2.1. Pivotal Study [305]

In the eribulin group, treatment-emergent increases in creatinine toxicity grades (TEAVs) occurred in Cycles 1, 2, and 3 with a respective incidence of 0.6% (n=3), 0.6% (n=3), and 0.2% (n=1) compared with corresponding incidences of 0.4% (n=1), 0.4% (n=1), and 0% (n=0) in the TPC group. Creatinine TEAVs occurred in only Cycles 1, 2, or 3.

8.6.2.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

Treatment-emergent abnormal increases in creatinine grades (TEAVs) were reported in 0.9% (11/1217) patients in the AETP group and 0.7% (6/827) patients in the BCP group.

8.6.3. Other clinical chemistry

8.6.3.1. Pivotal Study [305]

The incidence of TEAVs for all other clinical chemistry parameters was generally low (< 2%) in both the eribulin and TPC groups. The exceptions were in Cycle 1 in the eribulin group (eribulin vs TPC [n=235 chemotherapy treated patients]): hyponatraemia 3.0% (n=15) vs 1.3% (n=3); hyperphosphatemia 2.6% (n=13) vs 0.9% (n=2); and hypokalemia in 2.2% (n=11) vs 0.9% (n=2).

8.6.3.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

The most frequently reported chemistry laboratory TEAVs at any post-baseline visit over all cycles in the AETP and BCP groups are summarised below in Table 35.

Table 35: Abnormal chemistry laboratory values (TEAVs) over all cycles; safety population.

Laboratory Tests	All Eribulin Treated (N=1222) n (%)	Phase 2/3 Breast Cancer Subjects on Target Dose (N=827) n (%)
Hypophosphatemia	74/1160 (6.4)	49/ 796 (6.2)
Hyperglycemia[a]	29/ 566 (5.1)	13/ 322 (4.0)
Hyponatremia	61/1219 (5.0)	37/ 827 (4.5)
Alkaline Phosphatase	48/1212 (4.0)	36/ 825 (4.4)
Aspartate Aminotransferase	47/1218 (3.9)	37/ 826 (4.5)
Hypokalemia	43/1218 (3.5)	37/ 826 (4.5)
Alanine Aminotransferase	33/1218 (2.7)	28/ 826 (3.4)
Hypermagnesemia	26/1093 (2.4)	21/ 788 (2.7)
Hypocalcemia	22/1211 (1.8)	17/ 827 (2.1)
Hypoalbuminemia	21/1207 (1.7)	10/ 815 (1.2)
Hypercalcemia	18/1211 (1.5)	13/ 827 (1.6)
Hypernatremia	16/1219 (1.3)	16/ 827 (1.9)
Total Bilirubin increased	15/1218 (1.2)	9/ 826 (1.1)
Hyperkalemia	13/1218 (1.1)	9/ 826 (1.1)
Creatinine increased	11/1217 (0.9)	6/ 827 (0.7)
Hypomagnesemia	6/1093 (0.5)	6/ 788 (0.8)
Hypoglycemia	2/ 566 (0.4)	0/ 322 (0.0)

Percentages are based on the total number of subjects with non-missing lab measurement in relevant cycle and each integrated analysis set.

[a] Fasting was not required prior to blood sampling for glucose measurements.

TEAVs were defined as values which changed by at least 2 CTCAE grades from normal or Grade 1 at baseline.

8.6.4. Haematology

8.6.4.1. Pivotal Study [305]

8.6.4.1.1. Absolute Neutrophil Count (ANC)

In the eribulin group, in Cycle 1, of the 482 (96.8%) patients with baseline Grade 0 the number with post-baseline Grades 0, 1, 2, 3, and 4 were 147 (29.5%), 45 (9.0%), 90 (18.1%), 123 (24.7%) and 77 (15.5%), respectively. In Cycle 2, of the 461 (96.6%) patients with baseline Grade 0 the number with post-baseline Grades 0, 1, 2, 3, and 4 were 167 (35.0%), 51 (10.7%), 92 (19.3%), 89 (18.7%) and 62 (13.0%), respectively.

In the TPC chemotherapy group, in Cycle 1, of the 218 (94.4%) patients with baseline Grade 0 the number with post-baseline Grades 0. 1, 2, 3, and 4 were 138 (59.7%), 25 (10.8%), 28 (12.1%), 14 (6.1%), and 13 (5.6%), respectively. In Cycle 2, of the 191 (94.1%) patients with baseline Grade the number with post-baseline Grades 0, 1, 2, 3, and 4 were 130 (64.0%), 15 (7.4%), 20 (9.9%), 20 (9.9%), and 6 (2.3%), respectively.

In the eribulin group, during the entire treatment period, 138 (27.4%) patients and 135 (26.8%) patients had a shift in ANC from Grade 0 at baseline to Grade 3, and Grade 4, respectively (see Table 36, below). In the eribulin group, 143 (28.4%) and 144 (28.6%) patients during the study had a worst ANC grade of Grade 3, and Grade 4, respectively.

Table 36. Study 305 - ANC shift from baseline to worst Grade toxicity during eribulin treatment; safety population.

Baseline	Eribulin Treatment Group (n=503) – Worst Grade During Treatment, n (%)						
	0	1	2	3	4	Missing	Total
Grade 0	87 (17.3)	35 (7.0)	87 (17.3)	138 (27.4)	135 (26.8)	0	482 (95.8)
Grade 1	0	1 (0.2)	2 (0.4)	3 (0.6)	7 (1.4)	1 (0.2)	14 (2.8)
Grade 2	0	1 (0.2)	0	0	2 (0.4)	0	3 (0.6)
Grade 3	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0
Missing	1 (0.2)	0	0	2 (0.4)	0	1 (0.2)	4 (0.8)
Total	88 (17.5)	37 (7.4)	89 (17.7)	143 (28.4)	144 (28.6)	2 (0.4)	503 (100.0)

ANC – Grade 1 <LLN – 1.5 x 10^9 /L; Grade 2 <1.5 – 1.0 x 10^9 /L; Grade 3 <1.0 – 0.5 x 10_9 /L; Grade 4 <0.5 x 10^9 /L; Grade 5 death.

In the eribulin group, ANC TEAVs (i.e., values which changed by at least 2 CTCAE grades from normal or Grade 1 at baseline) occurred in 211 (41.9%) patients in Cycle 1, 158 (31.4%) in Cycle 2, and 80 (15.9%) patients in Cycle 3. In the TPC (total chemotherapy group), ANC TEAVs occurred in 28 (11.9%) and 27 (11.5%) patients in Cycles 1 and 2, respectively.

The time to ANC nadir and recovery from nadir was investigated using Kaplan-Meier estimates. The time to nadir was the earliest date of the minimum ANC value that was Grade 3 or 4, and patients who did not have a Grade 3 or 4 ANC value were censored. In the eribulin group, 287 (57.1%) patients had a nadir ANC (Grade 3 and 4) and the median time to nadir during the entire treatment period was 78 days [95% CI 57, 97]. The majority of patients recovered from the nadir (93.7%, n=269), and the median time to recovery to Grade 2 or lower was 8 days (up to 36 days). The mean time to nadir within a cycle ranged from approximately 12 days in Cycle 1 to 14 days in Cycle 7, and the median time to recovery to ≤ Grade 2 was 8 days for all cycles. In the TPC group, 58 (23.5%) patients had a nadir ANC (Grade 3 or 4), but the median time to nadir could not be estimated due to insufficient events. The majority of patients recovered from the nadir (94.8%, n=55). The median time to recovery to Grade 2 or lower was 8 days (up to 37 days).

In the eribulin group, decreases from baseline in mean and median neutrophil counts were observed, with the greatest decreases being reported in Cycle 1 and 2 (decrease in median of 1.6 x 10^9/L and 0.9 x 10^9/L, respectively). Decreases in the TPC group were also observed but were smaller.

> **Comment:** Increases in ANC toxicity occurred notably more commonly in the eribulin group than in the TPC group. In Cycle 1, in the eribulin group 24.7% and 15.5% of patients had a shift from Grade 0 at baseline to Grade 3 and 4, respectively, and the corresponding results for patients in the TPC (chemotherapy) group were 6.1% and 5.6%. In Cycle 2, the corresponding results in the eribulin group were 18.7% and 13.0%, and 9.9% and 2.3% in the TPC (chemotherapy group). ANC TEAVs also occurred more commonly in the eribulin group than in the TPC (chemotherapy) group, and the proportion of patients experiencing

a nadir (Grade 3 or 4) was greater in the eribulin group compared with the TPC (chemotherapy) group.

8.6.4.1.2. Leukopenia

In the eribulin group, in Cycle 1, of the 460 (92.0%) patients with baseline Grade 0 the number of patients with post-baseline leukopenia Grades 0, 1, 2, 3, and 4 were 100 (20.0%), 117 (23.4%), 140 (28.0%), 91 (18.2%), and 12 (2.4%), respectively. In Cycle 2, of the 441 (92.0%) patients with baseline Grade 0 the number of patients with post-baseline leukopenia Grades 0, 1, 2, 3, and 4 were 140 (29.2%), 99 (20.7%), 122 (25.5%), 76 (15.9%), and 4 (0.8%), respectively.

In the TPC group (chemotherapy), in Cycle 1, of the 214 (92.6%) patients with baseline Grade 0 the number of patients with post-baseline leukopenia Grades 0, 1, 2, 3, and 4 were 115 (49.8%), 46 (19.9%), 36 (15.5%), 15 (6.5%), and 2 (0.9%) respectively. In Cycle 2, of the 188 (92.6%) patients with baseline Grade 0 the number of patients with post-baseline leukopenia Grades 0, 1, 2, 3, and 4 were 98 (48.3%), 46 (22.7%), 31 (15,3%), 11 (5.4%), and 2 (1.0%), respectively.

Comment: The proportion of patients with baseline Grade 0 who shifted to post-baseline leukopenia Grades 2, 3, and 4, in Cycles 1 and 2, was as notably greater in the eribulin group than in the TPC group (chemotherapy).

8.6.4.1.3. Lymphocytopenia

In the eribulin group, in Cycle 1, of the 294 (59.3%) patients with baseline Grade 0 the number with post-baseline Grades lymphocytopenia 0, 1, 2, 3, and 4 were 200 (40.3%), 55 (11.1%), 32 (6.5%), 6 (1.2%), 1 (0.2%), respectively. In Cycle 2, of the 281 (59.4) patients with Grade 0 at baseline the number with post-baseline lymphocytopenia Grades 0, 1, 2, 3, and 4 were 191 (40.4%), 49 (10.4%), 32 (6.8%), 8 (1.7%), and 1 (0.2%), respectively.

In the TPC group (chemotherapy), in Cycle 1, of the 138 (60.2%) patients with baseline Grade 0 the with post-baseline lymphocytopenia Grades 0, 1, 2, 3, and 4 were 95 (41.5%), 28 (12.2%), 12 (5.2%), 3 (1.3%), and 0 (0%), respectively. In Cycle 2, of the 119 (58.9%) patients with Grade 0 at baseline the number with post-baseline lymphocytopenia Grades 0, 1, 2, 3, and 4 were 87 (43.1%), 19 (9.4%), 7 (3.5%, 6 (3.0%), and 0 (0%) respectively.

Comment: The proportion of patients with baseline Grade 0 who shifted to post-baseline lymphocytopenia Grades 2, 3, and 4, in Cycles 1 and 2, was similar in the eribulin and TPC group (chemotherapy) groups.

8.6.4.1.4. Haemoglobin

In the eribulin group, in Cycle 1, of the 318 (63.6%) patients with baseline grade 0 the number with post-baseline anaemia Grades 0, 1, 2, 3, and 4 were 127 (25.4%), 185 (37.0%), 127 (25.4%), 5 (1.0%), 0 (0%), and 1 (0.2%) respectively. In Cycle 2, of the 308 (64.3%) patients with Grade 0 at baseline the number with post-baseline anaemia Grades 0, 1, 2, 3, and 4 were 170 (35.5%), 131 (27.3%), 6 (1.3%), 1 (0.2%), and 0 (0%), respectively.

In the TPC (chemotherapy) group, in Cycle 1, of the 151 (65.4%) patients with baseline Grade 0 the number with post-baseline anaemia Grades 0, 1, 2, 3, and 4 were 97 (42.0%), 48 (20.8%), 5 (2.2%), 1 (0.4%), and 0 (0%), respectively. In Cycle 2, of the 134 (67.3%) patients with Grade 0 at baseline the number with post-baseline anaemia Grades 0, 1, 2, 3, and 4 were 73 (36.7%), 54 (27.1%), 7 (3.5%), 0 (0%), and 0 (0%), respectively.

Comment: In both the eribulin and TPC (chemotherapy) groups shifts from baseline 0 to post-baseline anaemia 2, 3, and 4 were infrequent in both Cycles 1 and 2, and there were no marked differences between the two groups.

8.6.4.1.5. Thrombocytopenia

In the eribulin group, in Cycle 1, of the 485 (97.2%) patients with baseline Grade 0 the number with post-baseline thrombocytopenia Grades 0, 1, 2, 3, and 4 were 445 (89.2%), 36 (7.2%), 1 (0.2%), 3 (0.6%), and 0 (0%), respectively. In Cycle 2, of the 466 (97.3%) patients with Grade 0 at baseline the number with post-baseline thrombocytopenia Grades 0, 1, 2, 3, and 4 were 427 (89.1%), 35 (7.3%), 2 (0.4%), 2 (0.4%), and 0 (0%), respectively.

In the TPC (chemotherapy) group, in Cycle 1, of the 215 (93.5%) patients with baseline Grade 0 the number with post-baseline thrombocytopenia Grades 0, 1, 2, 3, and 4 were 183 (79.6%), 29 (12.6%), 2 (0.9%), 1 (0.4%), and 0 (0%), respectively. In Cycle 2, of the 189 (93.1%) patients with baseline Grade 0 the number with post-baseline thrombocytopenia Grades 0, 1, 2, 3, and 4 were 165 (81.3%), 22 (10.8%), 0 (0%), 0 (0%), and 2 (1.0%), respectively.

> **Comment:** In both the eribulin and TPC (chemotherapy) groups shifts from baseline Grade 0 to post-baseline thrombocytopenia Grades 2, 3, and 4 were infrequent in both Cycles 1 and 2, and there were no marked differences between the two groups.

8.6.4.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

The changes in haematology parameters were similar in the AETP and BCP groups and were consistent with the changes in the eribulin treated group in the pivotal study. In the BCP group, the proportion of patients with haematological TEAVs were: ANC - 59.8% (493/825); WBC - 38.3% (317/827); 2.3% Hb - (19/82); and platelets - 1.5% (12/827). The results for shift from baseline Grade 0 to worst overall post-baseline Grades 0, 1, 2, 3, and 4 in the BCP group (all cycles combined) for the haematology parameters are summarised below in Table 37. Data on results for patients with baseline Grades 0-4 ANC, haemoglobin, lymphocytes, and platelets were also provided.

Table 37: BCP – Shift tables from baseline Grade 0 to worst overall post-baseline Grades all cycles combined; safety population.

Breast Cancer Population (BCP) – Baseline CTC Grade							
Baseline Grade 0	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Missing
ANC	135 (16.4%)	54 (6.6%)	135 (16.4%)	220 (26.8%)	250 (30.4%)	794 (96.6%)	0
Haemoglobin	169 (20.5%)	296 (35.9%)	41 (5.0%)	2 (0.2%)	1 (0.1%)	509 (61.8%)	0
Lymphocytes	151 (18.4%)	144 (17.6%)	80 (9.8%)	22 (2.7%)	5 (0.6%)	402 (49.0%	0
Platelets	659 (80.1%)	111 (13.5%)	8 (1.0%)	7 (0.9%)	2 (0.2%)	787 (95.6%)	0

8.6.5. Other laboratory test

8.6.5.1. Urinalysis

In the pivotal study [305], no summarised data were available on laboratory values outside the normal ranges for urinalysis in the safety population. However, examination of the mean change from baseline and shift tables for the AETP and BCP groups did not identify significant abnormalities in the urinalysis results in eribulin treated patients.

8.6.5.2. Electrocardiograph

8.6.5.2.1. Pivotal Study [305]

A standard 12-lead ECG was taken for all patients at screening and at study termination. In addition, patients randomised to eribulin treatment had an on-treatment ECG prior to starting Cycle 2. Clinically significant ECG changes at study termination were reported in 4 (0.6%) patients in the eribulin group and 2 (0.8%) patients in the TPC group. In the eribulin group, 1 of the 4 patients with an abnormal clinically significant ECG at termination also had an abnormal clinically significant ECG at baseline.

Patients with normal, or abnormal but not clinically significant, baseline ECGs, but abnormal clinically significant ECGs at study termination included: 1 eribulin treated patient with cardiac AEs of hypertension and atrial tachycardia developed ST depression; 1 eribulin treated patient with no reported cardiac AEs developed probable left ventricular hypertrophy; 1 eribulin treated patient with no reported cardiac AEs developed diffuse low voltage changes; 1 TPC (gemcitabine) treated patient with a reported AE of cardiac failure developed "cardiac insufficiency", and 1 TPC (capecitabine) treated patient with no reported AEs developed ventricular premature beats.

Examination of the mean and median changes from baseline to study termination in eribulin and TPC treated patients showed no notable abnormalities for the ECG parameters of PR interval, RR interval, QT interval, QTcB interval, QTcF interval, QRS interval, and heart rate.

8.6.5.3. Vital signs

8.6.5.3.1. Pivotal Study [305]

There were no marked changes in mean systolic blood pressure, diastolic blood pressure, heart rate, temperature or weight in either the eribulin group or the TPC group.

8.6.5.3.2. All eribulin treated patients (AETP) / Breast cancer population (BCP)

There were no notable changes over the duration of study in the AETP and BCP groups in systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, or temperature. In the AETP group, mean (SD) weight (kg) reductions from baseline ranged from 0.1 (1.6) to 2.6 (4.2) kg, and in the BCP group the reductions in weight from baseline were similar to those observed in the AETP group.

8.7. Safety issues with potential for major regulatory impact

8.7.1. Liver toxicity

There is no evidence in the submitted data that eribulin is associated with significant liver toxicity. No cases of DLI were observed when the ALT, AST, and TBL data were examined using criteria consistent those for Hy's Law. In the pooled data from the BCP group, treatment-emergent abnormal laboratory values (TEAVs) in ALT, AST, TBL, and SAP occurred in 3.4% (28/826), 4.5% (37/826), 1.1% (9/826), and 4.4% (36/825) of eribulin treated patients, respectively. The results for LFT TEAVs in the BCP group were similar to those in the AETP group.

In the pivotal study [305] (safety population), treatment-emergent hepatobiliary AE disorders (any) were reported in 32 (6.4%) patients in the eribulin group and 13 (5.3%) patients in the TPC group, while LFT laboratory test AEs were reported in 4 (2.2%) and 0 (0%) patients, respectively. In the eribulin group, hepatobiliary (any) disorders reported in the 32 patients were mainly hyperbilirubinaemia (n=9), hepatotoxicity (n=5), hepatomegaly (n=4), and jaundice (n=4). In the TPC group, hepatobiliary (any) disorders reported in the 13 patients were primarily hepatomegaly (n=5), hepatic pain (n=3), hyperbilirubinaemia (n=2), and jaundice

(n=2). Treatment emergent hepatobiliary disorders (irrespective of relationship to treatment) in the pivotal study [305] are summarised in the dossier.

Treatment-emergent hepatobiliary AE disorders (any term) leading to discontinuation were reported in 1 (0.2%) patient in the eribulin group (jaundice) and 1 (0.4%) patient in the TPC group (hepatic failure), while LFT laboratory test AEs leading to discontinuation were reported in 1 (0.2%) and 0 (0%) patients, respectively. Treatment emergent hepatobiliary serious AE disorders (any) were reported in 2 (0.2%) patients in the eribulin group (1 x bile duct obstruction, 1 x cytolytic hepatitis) and 2 (0.8%) patients in the TPC group (1 x hepatic failure, 1 x hyperbilirubinaemia). Fatal treatment emergent hepatobiliary AE disorders (any term) were reported in 1 (0.4%) patient in the TPC group (hepatic failure) and no patients in the eribulin group.

8.7.2. Haematological toxicity

There is a significant risk of neutropenia in eribulin treated patients. In the pivotal study [305] (safety population), haematological treatment emergent AEs of neutropenia, leukopenia, and anaemia occurred commonly in patients in both the treatment groups. Treatment emergent blood and lymphatic disorders (irrespective of relationship to treatment) in the pivotal study are summarised in the dossier.

8.7.3. Serious skin reactions

Eribulin is associated with a significant risk of alopecia. In the pivotal study [305] (safety population), alopecia occurred in 44.5% (n=224) of patients in the eribulin group and 9.7% (n=24) of patients in the TPC group. Overall, skin and subcutaneous tissue disorders (any) occurred more frequently in patients in the eribulin group (52.9%, n=266) compared with the TPC group (32.0%, n=79), due primarily to the greater number of patients with alopecia.

In the pivotal study [305] (safety population), palmar plantar erythrodysaesthesia syndrome occurred notably more frequently in patients in the TPC group (5.7%, n=14) than in patients in the eribulin group (1.4%, n=7). The only other skin and subcutaneous disorder occurring in ≥ 5% of patients in either treatment group (eribulin vs TPC) was rash (6.2%, n=31 vs 6.1%, n=15, respectively). Treatment-emergent serious AEs occurred in 3 (0.6%) patients in the eribulin group (1 x palmar plantar erythrodysaesthesia, 1 x rash, and 1 x angioedema) and 1 (0.5%) patient in the TPC group (1 x palmar plantar erythrodysaesthesia). Treatment-emergent skin reaction AEs leading to discontinuation occurred in 5 (2.0%) patients in the TPC group (4 x palmar plantar erythrodysaesthesia, 1 x rash, 1 x skin toxicity), and no patients in the eribulin group.

8.7.4. Cardiovascular safety

In the pivotal study [305], patients with significant cardiovascular impairment were excluded from the study (i.e., history of NYHA > Grade 2, unstable angina, or myocardial infarction within the previous 6 months, or serious cardiac arrhythmias). Treatment emergent cardiac disorders (any) occurred marginally more commonly in patients in the eribulin group (6.6%, n=33) than in patients in the TPC group (4.0%, n=33). Both tachycardia and palpitations occurred more frequently in the eribulin group than in the TPC group: tachycardia 3.6%, n=18 vs 1.2%, n=3, respectively, and palpitations 1.6%, n=8 vs 0.4%, n=1, respectively. Arrhythmia was reported in 1 (0.2%) patient in the eribulin group and 1 (0.4%) patient in the TPC group, and atrial fibrillation and atrial tachycardia were both reported in 1 (0.2%) patient in the eribulin group and no patients in the TPC group. There were no reports of Torsade de pointes in either treatment group. There were 3 patients with treatment-emergent serious AEs in the eribulin group (2 x pericardial effusion, 1 x cardiac failure) compared with no patients in the TPC group. There were no patients in either treatment group with cardiac disorders leading to discontinuation. There was 1 (0.5%) patient with a treatment-emergent AE (investigations) of cardiac murmur (CTCAE Grade 1) in the eribulin group compared with no patients in the TPC

group. Treatment emergent cardiac disorders (irrespective of relationship to treatment) in the pivotal study are summarised in the dossier.

In the pivotal study [305] (safety population), treatment emergent vascular disorder (any) occurred more commonly in patients in the eribulin group (16.3%, n=82) than in patients in the TPC group (13.0%, n=32). In the eribulin group (vs the TPC) group, there were higher incidences of hypertension (3.6%, n=18 vs 1.6%, n=4), hot flush (2.8%, n=14 vs 2.0%, n=5), and hypotension (2.6%, n=13 vs 1.6%, n=4). There were 2 (0.4%) patients with deep vein thrombosis in the eribulin group compared with 3 (1.2%) in the TPC group, and the respective figures for embolism were 1 (0.2%) and 2 (0.8%) patients. Discontinuations due to vascular disorders were reported in 1 (0.2%) patient in the eribulin group (1 x deep vein thrombosis) and no patients in the TPC group. Fatal treatment-emergent vascular disorders (any) were reported in 1 (0.2%) patient in the eribulin group (cardiovascular insufficiency) and 2 patients in the TPC group (1 x cardiovascular insufficiency;1 x embolism). Treatment emergent vascular disorders (irrespective of relationship to treatment) in the pivotal study are summarised in the dossier.

In the pivotal study [305] (safety population), treatment-emergent pulmonary embolism (Respiratory, Thoracic, and Mediastinal Disorders SOC) occurred with similar frequencies in both the eribulin group (1.8%, n=9) and the TPC group (2.0%, n=5). The incidence of treatment-emergent serious AEs of pulmonary embolism was 1.4% (n=7) in the eribulin group and 1.2% (n=3) in the TPC group. There was 1 treatment-emergent fatal pulmonary embolus reported in both treatment groups (0.2% in the eribulin group and 0.4% in the TPC group).

In the pooled analyses, cardiac events were reported in 8.9%(n=108) of patients in the AETP group, and 7.6% (n=63) of patients in the BCP group. Treatment-emergent cardiac disorder reported with the highest incidence (AEPT vs BCP) were tachycardia (4.0%, n=49 vs 3.6%, n=30), and palpitation (1.9%, n=23 vs 1.8%, n=15). Other treatment-emergent cardiac disorders occurred with an incidence of < 1.0% in both eribulin treatment groups. In the AETP group, there were very few treatment-related cardiac AEs adverse, and the majority were tachycardia (15, 13 of which were Grade 1) and palpitations (9, 8 of which were Grade 1).

8.7.5. Unwanted immunological events

Treatment-emergent immune system disorders (any) AEs were reported infrequently in patients in both the eribulin group (2.0%, n=10) and the TPC group (1.3%, n=3). The most commonly reported immune system disorder TEAE in the eribulin group was hypersensitivity (1.0%, n=5) and this event was not reported in the TPC group.

8.8. Other safety issues

8.8.1. Safety in special populations

Race

In the AETP and BCP groups, there were no notable differences in the safety profile of eribulin by race (Black or African American, White, Asian/Pacific Islander, Other). However, in both the AETP and BCP groups, the majority of patients were White (82.6% and 83.0%, respectively). Consequently, the safety analyses based on race should be interpreted cautiously due to the significant imbalance in patient numbers among the racial groups.

Age

The AETP and BCP groups, included an assessment of the safety profile of eribulin by age group (≤ 40, > 40 to 55, > 55 to 65, > 65 to 75, > 75). Examination of the BCP group showed no difference among the age groups in TEAEs (nearly all patients in all age groups experienced at least one TEAE). However, women aged > 75 years were reported as experiencing fewer treatment related TEAEs and serious TEAEs than women in the other age groups, but these

results should be interpreted cautiously as the BCP group included only 17 patients aged > 75 years (2.1%).

8.8.2. Safety related to drug-drug interactions and other interactions

Safety related to drug-drug and/or other interactions was not examined in the pivotal study [305]. There were a number of analyses in the AETP and BCP groups relating to drug-drug and drug-disease interactions. However, in the absence of a comparator group it is difficult to draw meaningful conclusions from these descriptive, exploratory, subgroup analyses.

8.9. Evaluator's overall conclusion on clinical safety

- The primary focus on safety in this report has been on the data from the safety population in the pivotal Phase III study [305] consisting of 750 patients (n=503, eribulin; n=247, TPC). The safety data in the pivotal study in eribulin treated patients (n=503) is consistent with the pooled safety data in the AETP group (n=1222) from 11 Phase I/II/III studies, and the pooled safety data in the BCP group (n=827) from the pivotal Phase III study [305] and 2 Phase II supportive studies [201, 211]. This observation is not surprising, given the considerable overlapping of patients among the three safety populations.
- In the pivotal study, nearly all patients in both the eribulin (98.8%, n=487) and the TPC (93.1%, n=230) groups experienced at least one AE (irrespective of relationship to treatment). The most frequently reported AEs (≥ 20%) in patients in either treatment group (eribulin vs TPC) were asthenia/fatigue (53.7%, n=270 vs 39.7%, n=98), neutropenia (51.7%, n=260 vs 29.6%, n=73) alopecia (44.5%, n=224 vs 9.7%, n=24), peripheral neuropathy (34.6%, n=174 vs 16.2%, n=40), nausea (34.6%, n=174 vs 28.3%, n=70), constipation (24.7%, n=124 vs 20.6%, n=51), leukopenia (23.1%, n=116 vs 11.3%, n=28), arthralgia/myalgia (21.7%, n=109 vs 11.7%, n=29), weight decreased (21.3%, n=107 vs 14.2%, n=35), pyrexia (20.9%, n=105 vs 12.6%, n=31), and anaemia (18.7%, n=94 vs 22.7%, n=56).
- The majority of the commonly reported AEs (≥ 20%) in either treatment group were CTCAE Grade 1 or 2. However, in the eribulin group (vs TPC), there were four CTCAE Grade 3 events reported with an incidence of ≥ 5% (neutropenia 21.1%, n=106 vs 14.2%, n=35; leukopenia 11.7%, n=59 vs 4.9%, n=12; asthenia/fatigue 8.2%, n=41 vs 10.1%, n=25; peripheral neuropathy 7.8%, n=39 vs 2.0%, n=5), and one CTCAE Grade 4 event reported with an incidence of ≥ 5% (neutropenia 24.1%, n=121 vs 6.9%, n=17).
- AEs occurring with an incidence of ≥ 10% but < 20% in patients in the eribulin group, and ≥ 2% more commonly than in patients in the TPC group were anorexia (19.5%, n=98 vs 13.0%, n=32), headache (19.3%, n=97 vs 11.7%, n=29), dyspnoea (15.7%, n=79 vs 12.6%, n=31), back pain (15.7%, n=79 vs 7.3%, n=18), arthralgia (13.7%, n=69 vs 5.3%, n=13), peripheral sensory neuropathy (12.3%, n=62 vs 4.0%, n=10), bone pain (11.9%, n=60 vs 9.3%, n=23), paraesthesia (11.1%, n=56 vs 6.5%, n=16), and myalgia (10.7%, n=54 vs 6.9%, n=17).
- The frequent AEs (any) in both treatment groups (eribulin vs TPC) appear to have been managed by dose delays (35.2%, n=177 vs 32.4%, n=80), dose reductions (16.9%, n=85 vs 15.8%, n=39), and dose interruptions (5.0%, n=25 vs 10.1%, n=25), rather than treatment discontinuation (13.3%, n=67vs 15.4%, n=38). The two most common AEs (≥ 1%) leading to treatment discontinuation in the eribulin group (vs TPC) were peripheral neuropathy (4.8%, n=24 vs 1.2%, n=3), and asthenia/fatigue (1.8%, n=9 vs 1.6%, n=4). All other AEs in the eribulin group leading to discontinuation occurred with an incidence of < 1%.
- In the pivotal study, each of the two haematological AEs of special interest (neutropenia and febrile neutropenia) and the four non-haematological AEs of special interest

(asthenia/fatigue, alopecia, peripheral neuropathy, and arthralgia/myalgia) occurred notably more frequently in patients in the eribulin group compared with the TPC group.

- SAEs leading to death during the study or within 30 days of last study treatment occurred in 4.0% (n=20) of patients in the eribulin group and 7.3% (n=18) of patients in the TPC group. SAEs (fatal and others) were reported in 25.0% (n=126) of eribulin-treated patients and 25.9% (n=64) of patients in the TPC group. The most frequently reported SAEs in the eribulin group (vs the TPC group) was febrile neutropenia (4.2%, n=21 vs 1.2%, n=3). Fatal SAEs were reported as treatment-related in 5 (1.0%) patients in the eribulin group and 2 (0.8%) patients in the TPC group.
- The most commonly reported haematological AE in both treatment groups was neutropenia, and this AE was reported more frequently in patients in the eribulin group (51.7%, n=260) than in the TPC group (29.6%, n=73). Furthermore, in both the eribulin and the TPC groups, neutropenia was the most frequently reported CTCAE Grade 3 event (21.1%, n=106 and 14.2%, n=35, respectively) and CTCAE 4 event (24.1%, n=121 and 6.9%, n=17, respectively). Febrile neutropenia was reported less frequently than neutropenia in both the eribulin group (4.6%, n=23) and the TPC group (1.6%, n=4), but all cases were CTCAE Grade 3, 4, or 5 events. The two most common SAEs in patients in the eribulin group (vs TPC group) were febrile neutropenia (4.2%, n=21 vs 1.2%, n=3), and neutropenia (1.8%, n=9 vs 0%). There were 2 fatal serious TEAEs due to febrile neutropenia reported as being treatment-related occurring within 30 days of the last dose (1 in each treatment group).
- Neutropenia leading to discontinuation occurred in only 3 patients (0.6%) in the eribulin group and no patients in the TPC group. However, neutropenia resulting in discontinuation, delay or dose reduction occurred in 114 (27.2%) patients in the eribulin group and 46 (18.6%) patients in TPC group. These results indicate that neutropenia in both treatment groups was primarily managed by dose delays or reductions rather than treatment discontinuation. In addition, neutropenia appears to have been commonly managed with C-CSF. In the eribulin group C-CSF, pegfilgastrim, and GM-CSF were administered to 17.7% (n=89), 2.4% (n=12), and 0.2% (n=1) of patients, respectively, and the corresponding values in the TPC group were 7.7% (n=19), 3.2% (n=8), and 0 (0%).
- During the pivotal study, 82.5% (n=415) of eribulin treated patients had a laboratory test ANC of CTCAE Grade 1 or above. In eribulin treated patients, the ANC shifted from baseline CTCAE Grade 0 (95.8%, n=482) to worst CTCAE Grade 3 in 27.4% (n=138) of patients, and worst CTCAE Grade 4 in 26.8% (n=135) of patients. In eribulin treated patients (n=503), worst grade CTCAE ANC Grade 3 and 4 occurred in 28.4% (n=143) and 28.6% (n=144) of patients, respectively, In the eribulin group, 287 (57.1%) patients had a nadir ANC (CTCAE Grade 3 or 4). The mean time to CTCAE Grade 3/4 nadir within a cycle was approximately 13 days, and the majority of patients recovered from the nadir (93.7%, n=269), with a median time to recovery to ≤ CTCAE Grade 2 of about 8 days.
- In the pivotal study, the AE of anaemia was reported in 18.7% (n=94) of patients in the eribulin group and 22.7% (n=56) of patients in the TPC group, with more than 80% of patients in both groups experiencing CTCAE Grade 1 or 2 events. Discontinuation due to anaemia AEs occurred in 1 (0.2%) patient in the eribulin group and no patients in the TPC group. In the pooled BCP data, of the 509 patients with baseline laboratory haemoglobin CTCAE Grade 0, 340 (66.9%) experienced a post-baseline shift to CTCAE Grade 1 or above with the majority of patients shifting only to CTCAE Grade 1 (296/340 [87.1%]). The AE of thrombocytopenia was reported infrequently in both the eribulin (2.6%, n=13) and the TPC (4.9%, n=12) groups, and discontinuations due to this AE occurred in only 1 (0.2%) patient in the eribulin group and 2 (0.8%) patients in the TPC group. In the pooled BCP data, of the 787 patients with baseline laboratory platelets CTCAE Grade 0, 128 (16.3%) experienced a post-baseline shift to CTCAE Grade 1 or above with nearly all of these patients (86.7%, 111/128) shifting to CTCAE Grade 1. The AE of pancytopenia was reported in only 1 (0.2%)

eribulin treated patient (CTCAE Grade 4 event), but did not result in treatment discontinuation.

- The major non-haematological safety concern associated with eribulin is the development of peripheral neuropathy. In the pivotal study, patients with pre-existing neuropathy > CTCAE Grade 2 were excluded from the study. Peripheral neuropathy was reported in 34.6% (n=174) of patients in the eribulin group and 16.2% (n=40) of patients in the TPC group. In both treatment groups, the majority of patients with peripheral neuropathy experienced CTCAE Grade 1 or 2 events. Peripheral neuropathy was the most commonly reported AE leading to treatment discontinuation in eribulin treated patients (4.8%, n=24 vs 1.2%, n=3 [TPC]), and discontinuations, delays or dose reductions due to this events occurred in 8.5% (n=43) of eribulin treated patients. Overall, the data suggest that treatment continued in about 90% of eribulin treated patients who developed peripheral neuropathy, and that most of these patients did not require dose reductions or delays.
- Kaplan-Meier analysis in the pivotal study estimated that the risk of peripheral neuropathy developing or progressing to ≥ Grade 2 during treatment in patients without baseline disease or set to Grade 1 in patients with missing baseline data was 2.3-fold higher in the eribulin group than in the TPC group. In this analysis, the 1-year rate for development/progression of peripheral neuropathy was higher in patients in the eribulin group (21.4%) compared with the TPC group (9.5%), and the respective 2-year rates were 23.1% and 9.5%.
- In the BCP group, there were 288 (34.8%) patients with treatment emergent peripheral neuropathy (any), and at the time of follow-up after last treatment resolution had occurred in only 14.2% (n=41) with a median time to resolution of 8.1 weeks. In this patient population the median time to onset of peripheral neuropathy was 23.4 weeks. In a sub-group analysis in the BCP group, the incidence of peripheral neuropathy was similar in eribulin treated patients without pre-existing neuropathy, with Grade 1 pre-existing neuropathy, and with Grade ≥ 2 pre-existing neuropathy (31.5% [197/625], 34.5% [49/142], and 29.6% [8/27], respectively).
- In the pivotal study, each of the two haematological AEs of special interest (neutropenia, febrile neutropenia) and the four non-haematological AEs of special interest (asthenia/fatigue, alopecia, peripheral neuropathy, arthralgia/myalgia) occurred notably more commonly in patients in the eribulin group compared with the TPC group. The risk of cardiovascular AEs (cardiac disorders and vascular disorders) occurred marginally more commonly in patients in the eribulin group than in the TPC group. However, there does not appear to be an increased risk of hepatic, renal or immune system toxicity with eribulin compared with TPC.
- In the pivotal study, exposure to both treatments is considered adequate to allow for satisfactory comparative evaluation of the safety profiles of the two treatments in the proposed patient population. However, the median duration of exposure in the eribulin group (118.0 days) was longer than in the TPC group (n=64.0 days). This difference in exposure duration might, at least in part, accounted for the higher incidence of TEAEs in the eribulin group than in the TPC group. However, *post hoc* analyses provided in the Summary of Clinical Safety [Module 2.7.4] to evaluate the effect of the difference in median duration of exposure between the two treatment groups on selected subgroups are considered to confirm the greater risk associated with eribulin compared with TPC. In both *post analyses* (100 subject days of treatment exposure and first 8 weeks of the treatment period), the incidence of neutropenia, febrile neutropenia, peripheral anaemia, and alopecia was greater in the eribulin treated group than in the TPC group. In addition, the incidence of asthenia/fatigue and nausea was greater in the eribulin group in the first 8 weeks of treatment than in the TPC group. The results for the post hoc analyses per 100 subject-days and in the first 8 weeks of treatment are provided in the dossier.

- The TPC group included 238 chemotherapy treated patients and 9 hormonal treated patients. The pivotal study included *post hoc* subgroup analyses comparing the safety of eribulin and the 5 most commonly used chemotherapy agents in the TPC group. The comparative safety data from these subgroup analyses are considered to be exploratory rather than definitive as the study was specifically designed to compare eribulin with the total TPC population.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

In the pivotal study [305], eribulin (n=508) at the proposed dose showed a clinically meaningful and statistically significant median OS benefit of 2.5 months [95% CI: 0.7, 4.3] compared with TPC (n=254) in the original data, and 2.7 months [95% CI: 1.0, 4.5] in the updated (more mature) data. However, the OS benefit observed with eribulin relative to TPC is small and is considered to be at the lower limit of meaningful clinical benefit. The study was powered to detect a difference in median OS of 3 months in favour of eribulin (OS estimated to be 12 months) compared with TPC (OS estimated to be 9 months). Consequently, it can be inferred that the sponsor considered a median OS benefit of 3 months in favour of eribulin relative to TPC to be the minimum clinically meaningful difference.

In the pivotal study [305], in the original data (ITT population) median OS (primary efficacy variable) was 399 days [95% CI: 360, 434] in patients in the eribulin group and 324 days [95% CI: 282, 380] in the TPC group: HR [erib:tpc] = 0.809 [95% CI: 0.660, 0.991], p=0.041 (stratified log-rank test). Median OS was 75.0 days [95% CI: 21.4, 128.6] longer in patients in the eribulin group compared with the TPC group. In the updated data (ITT population), median OS was 403 days [95% CI: 367, 438] in patients in the eribulin group and 321 days [95% CI: 281, 365] in the TPC group: HR [erib:tpc] = 0.805 [95% CI: 0.667, 0.958], p=0.014 (stratified log-rank test). Median OS was 82 [95% CI: 29.9, 134.1] days longer in patients in the eribulin group compared with the TPC group. In both the original and updated OS analyses, the HR was based on a Cox model stratified for HER2/*neu* status, prior capecitabine treatment, and geographical region.

In the pivotal study [305], death occurred in 53.9% (n=274) patients in the eribulin group and 58.3% (n=148) of patients in the TPC group in the original data (i.e., 55.4% [422/762] of all enrolled patients), and the corresponding figures were 76.0% (n=386) and 79.9% (n=203) in the updated patients (i.e., 77.3% [589/762] of all enrolled patients).

In the pivotal study [305[, in the primary analysis (*Independent review*) the median PFS (secondary efficacy variable) in the ITT population was 45 days longer in patients in the eribulin group compared with patients in the TPC group: 113 [95% CI: 101, 118] and 68 [95% CI: 63, 103] days, respectively). However, the difference in median PFS between the two treatment groups was not statistically significant: HR [erib:tpc] = 0.865 [95% CI: 0.714, 1.048]; p=0.137 (stratified log-rank test). In a sensitivity analysis (*Investigator review*) using different censoring rules for disease progression, the median difference in PFS between the two groups was 44 days in favour of patients in the eribulin group compared with the TPC group: HR = 0.788 [95% CI: 0.644, 0.964; p = 0.020 (stratified log-rank test). The median PFS benefits can be considered to be clinically equivalent for the two analyses eventhough the statistical results were inconsistent (i.e., 45 days [not statistically significant], primary analysis and 44 days [statistically significant], sensitivity analysis). Overall, the median PFS benefit can be considered to be consistent with the median OS benefit (i.e., both in favour of eribulin).

In the pivotal study, the ORR (secondary efficacy variable) was statistically significantly higher in the eribulin group compared with the TPC group based on *Independent review* (12.2% [95% CI: 9.4, 12.5] and 4.7% [95% CI: 2.3, 8.4]; p=0.002 (Fisher's exact test). The major contributor to

the ORR in both treatment groups was the PR (11.5% and 4.7%, eribulin and TPC groups respectively) with CR being 0.6% in the eribulin group and 0% in the TPC group. The sensitivity analysis of the ORR based on *Investigator review* was consistent with the primary analysis based on *Independent review*. Overall, the ORR is considered to support the OS and PFS analyses.

In the pivotal study [305], there was no statistically significant difference in the median DoR (secondary efficacy variable) between the eribulin and TPC treatment groups. However, the number of patients included in the TPC group are considered too small to provide a meaningful comparison for DoR between the two treatment groups.

The submission did not include any studies specifically comparing the benefits (efficacy) of eribulin with those of capecitabine and/or vinorelbine. In Australia, the approved indications of both capecitabine and vinorelbine can support their use as third-line monotherapy for patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens (which should have included an anthracycline and a taxane). Therefore, in the absence of pivotal efficacy data comparing eribulin with capecitabine/and or vinorelbine an argument can be made for relegating eribulin from third-line to fourth-line (or fifth-line) treatment for the proposed indication behind taxanes, anthracyclines, and capecitabine and/or vinorelbine. However, there is no evidence from the published data that either capecitabine or vinorelbine as monotherapy offer an overall survival benefit for the proposed usage. Consequently, it is considered that the observed OS benefit of eribulin compared with TPC in the pivotal study is enough to support the approval of the drug as an alternative monotherapy to capecitabine and/or vinorelbine, without the need for pivotal efficacy data comparing eribulin with capecitabine and/or vinorelbine.

9.2. First round assessment of risks

Overall, the safety data from the pivotal study [305] are considered to show that the risk to women in the proposed patient population treated with eribulin is greater than the risk to women treated with TPC. The assessment of the risks associated with eribulin described below are based on assessment of the pivotal study [305], unless otherwise stated. The safety profile of eribulin in the pivotal study is consistent with those with eribulin in other submitted studies.

In the pivotal study, nearly all patients in both the eribulin group (98.8%, n=487) and the TPC group (93.1%, n=230) experienced at least one AE (irrespective of relationship to treatment). However, patients in the eribulin group (n=503) were at greater risk than patients in the TPC group (n=247) for the following most commonly reported AEs (i.e., events occurring with a frequency of ≥ 20% in either treatment group): asthenia/fatigue (53.7%, n=270 vs 39.7%, n=98); neutropenia (51.7%, n=260 vs 29.6%, n=73); alopecia (44.5%, n=224 vs 9.7%, n=24); peripheral neuropathy (34.6%, n=174 vs 16.2%, n=40); nausea (34.6%, n=174 vs 28.3%, n=70); constipation (24.7%, n=124 vs 20.6%, n=51); leukopenia (23.1%, n=116 vs 11.3%, n=28), arthralgia/myalgia (21.7%, n=109 vs 11.7%, n=29); weight decreased (21.3%, n=107 vs 14.2%, n=35), and pyrexia (20.9%, n=105 vs 12.6%, n=31). The only AE reported with a frequency of ≥ 20% in either treatment group that occurred more frequently in TPC treated patients than in eribulin treated patients was anaemia (22.7%, n=56 vs 18.7%, n=94, respectively).

Furthermore, AEs occurring with an incidence of ≥ 10% but < 20% in patients in the eribulin group, and ≥ 2% more commonly than in patients in the TPC group were: anorexia (19.5%, n=98 vs 13.0%, n=32); headache (19.3%, n=97 vs 11.7%, n=29); dyspnoea (15.7%, n=79 vs 12.6%, n=31); back pain (15.7%, n=79 vs 7.3%, n=18); arthralgia 13.7%, n=69 vs 5.3%, n=13); peripheral sensory neuropathy (12.3%, n=62 vs 4.0%, n=10); bone pain (11.9%, n=60 vs 9.3%, n=23); paraesthesia (11.1%, n=56 vs 6.5%, n=16); and myalgia (10.7%, n=54 vs 6.9%, n=17).

The majority of the most commonly reported AEs (i.e., events occurring with a frequency of ≥ 20% in either treatment group) were CTCAE Grade 1 or 2. However, in the eribulin group (vs TPC) there were four CTCAE Grade 3 events reported with an incidence of ≥ 5% (neutropenia

21.1%, n=106 vs 14.2%, n=35; leukopenia 11.7%, n=59 vs 4.9%, n=12; asthenia/fatigue 8.2%, n=41 vs 10.1%, n=25; peripheral neuropathy 7.8%, n=39 vs 2.0%, n=5), and one CTCAE Grade 4 event reported with an incidence of ≥ 5% (neutropaenia 24.1%, n=121 vs 6.9%, n=17).

The frequent AEs (any) in both treatment groups (eribulin vs TPC) appear to be able to be managed by dose delays (35.2%, n=177 vs 32.4%, n=80), dose reductions (16.9%, n=85 vs 15.8%, n=39), and dose interruptions (5.0%, n=25 vs 10.1%, n=25), rather than treatment discontinuation (13.3%, n=67vs 15.4%, n=38). In addition, the use of symptomatic medication to manage specific adverse events such as nausea and vomiting also appears to have been high in both treatment groups (eribulin vs TPC): e.g. dexamethasone 38.2%, n=192 vs 34.0%, n=84; ondansetron 31.4%, n=158 vs 23.5%, n=58; metoclopramide 15.9%, n=80 vs 17.4%, n=43; granisetron 13.5%, n=68 vs 8.1%, n=20; and palonosetron 4.6%, n=23 vs 2.8%, n=7. The two most common AEs (≥ 1%) leading to treatment discontinuation in the eribulin group (vs TPC) were peripheral neuropathy (4.8%, n=24 vs 1.2%, n=3), and asthenia/fatigue (1.8%, n=9 vs 1.6%, n=4). All other AEs in the eribulin group leading to discontinuation occurred with an incidence of < 1%.

At the data cut-off date of 12 May 2009 (original data), in the safety population there had been 271 (53.9%) deaths in the eribulin group and 143 (57.9%) deaths in the TPC group. The primary reason for death was progressive disease in both the eribulin group (50.5%, n=254) and the TPC group (54.7%, n=135). SAEs leading to death during the study or within 30 days of last study treatment occurred less commonly in patients in the eribulin group (4.0%, n=20) than in the TPC group (7.3%, n=18). Fatal SAE was reported as treatment-related in 5 (1.0%) patients in the eribulin group (2 x dyspnoea, febrile neutropenia lung infection bronchopneumonia) and 2 (0.8%) patients in the TPC group (aspergillosis, febrile neutropenia). SAEs (fatal and others) were reported in 25.0% (n=126) of eribulin-treated patients and 25.9% (n=64) of patients in the TPC group. The most frequently reported SAEs in the eribulin group (vs the TPC group) was febrile neutropenia (4.2%, n=21 vs 1.2%, n=3).

Neutropenia was the most commonly reported haematological AE in both treatment groups, and was reported more frequently in patients in the eribulin group (51.7%, n=260) than in the TPC group (29.6%, n=73). Furthermore, in both the eribulin and the TPC groups, neutropenia was the most commonly reported CTCAE Grade 3 event (21.1%, n=106 and 14.2%, n=35, respectively) and CTCAE 4 event (24.1%, n=121 and 6.9%, n=17, respectively). Febrile neutropenia was reported less frequently than neutropenia in both the eribulin group (4.6%, n=23) and the TPC group (1.6%, n=4), but all cases were CTCAE Grade 3, 4, or 5 events. The two most common SAEs in patients in the eribulin group (vs TPC group) were febrile neutropenia (4.2%, n=21 vs 1.2%, n=3), and neutropenia (1.8%, n=9 vs 0%)). There were 2 fatal serious TEAEs due to febrile neutropenia reported as being treatment related (1 in each treatment group) occurring within 30 days of the last dose.

Neutropenia leading to discontinuation occurred in only 3 patients (0.6%) in the eribulin group and no patients in the TPC group. However, neutropenia resulting in discontinuation, delay or dose reduction occurred more commonly in patients in the eribulin group (27.2%, n=114) than in the TPC group (18.6%, n=46). These results indicate that neutropenia in both treatment groups was primarily managed by dose delays or reductions rather than treatment discontinuation. In addition, the data indicate that neutropenia was also managed with colony stimulating factors. In the eribulin group C-CSF, pegfilgastrim, and GM-CSF were received by 17.7% (n=89), 2.4% (n=12), and 0.2% (n=1) of patients, respectively, and the corresponding values in the TPC group were 7.7% (n=19), 3.2% (n=8), and 0 (0%).

During the pivotal study, 82.5% (n=415) of eribulin treated patients had a laboratory test ANC of CTCAE Grade 1 or above. In eribulin treated patients, the ANC shifted from baseline CTCAE Grade 0 (95.8%, n=482) to worst CTCAE Grade 3 in 27.4% (n=138) of patients and worst CTCAE Grade 4 in 26.8% (n=135) of patients. In eribulin treated patients (n=503), worst grade CTCAE ANC Grade 3 and 4 occurred in 28.4% (n=143) and 28.6% (n=144) of patients, respectively. In

the eribulin group, 287 (57.1%) patients had a nadir ANC (CTCAE Grade 3 or 4). The mean time to CTCAE Grade 3/4 nadir within a cycle was approximately 13 days, and the majority of patients recovered from the nadir (93.7%, n=269), with a median time to recovery to ≤ CTCAE Grade 2 of about 8 days.

In the pivotal study, the AE of anaemia was reported in 18.7% (n=94) of patients in the eribulin group and 22.7% (n=56) of patients in the TPC group, with more than 80% of patients both groups experiencing CTCAE Grade 1 or 2 events. Discontinuation due to anaemia AEs occurred in 1 (0.2%) patient in the eribulin group and no patients in the TPC group. Discontinuations, delay or dose reduction occurred in 10 (n=2.0%) patients with anaemia in the eribulin group and in 3 (1.2%) patients in the TPC group. In the pooled BCP data, of the 509 patients with baseline laboratory haemoglobin CTCAE Grade 0, 340 (66.9%) experienced a post-baseline shift to CTCAE Grade 1 or above with the majority of patients shifting only to CTCAE Grade 1 (296/340 [87.1%]). Overall, the data suggest that most patients who develop anaemia while being treated with eribulin do not require dose modification. Treatments used to manage anaemia during the study included (eribulin vs TPC): darbepoetin alfa (24, 4.8% vs 11, 4.5%); erythropoietin human (14, 2.8% vs 2.8%, n=7); erythropoietin (3, 0.6% vs 3, 1.2%); and red blood cells (11, 2.2% vs 7, 2.8%).

The AE of thrombocytopenia was reported infrequently in both the eribulin (2.6%, n=13) and the TPC (4.9%, n=12) groups. Discontinuations due to this AE occurred in 1 (0.2%) patient in the eribulin group and 2 (0.8%) patients in the TPC group, and the corresponding patient numbers for discontinuation, delay, or dose reduction were 5 (1.0%) and 5 (2.0%). In the pooled BCP data, of the 787 patients with baseline laboratory platelets CTCAE Grade 0, 128 (16.3%) experienced a post-baseline shift to CTCAE Grade 1 or above with nearly all patients (n=111) shifting to CTCAE Grade 1. The AE of pancytopenia was reported in 1 (0.2%) eribulin treated patient only (CTCAE Grade 4 event), but did not result in treatment discontinuation.

The major non-haematological safety concern associated with eribulin is the development of peripheral neuropathy. In the pivotal study, peripheral neuropathy was identified as one of the four non-haematological AEs of special interest. In the pivotal study, patients with pre-existing neuropathy > CTCAE Grade 2 were excluded from the study. Peripheral neuropathy was reported in 34.6% (n=174) of patients in the eribulin group and 16.2% (n=40) of patients in the TPC group. In both treatment groups, the majority of patients with peripheral neuropathy experienced CTCAE Grade 1 or 2 events. Peripheral neuropathy was the most commonly reported AE leading to treatment discontinuation in eribulin treated patients (4.8%, n=24 vs 1.2%, n=3 [TPC]), and discontinuations, delays or dose reductions occurred in 8.5% (n=43) of eribulin treated patients. Overall, the data suggest that treatment continued in about 90% of eribulin treated patients who developed peripheral neuropathy, and that most of these patients did not require dose reductions or delays despite ongoing peripheral neuropathy.

Kaplan-Meier analysis of peripheral neuropathy in the pivotal study estimated that the risk of this event developing or progressing during treatment (≥ Grade 2) was 2.3-fold higher in the eribulin group than in the TPC group in patients with no baseline peripheral neuropathy or baseline set to Grade 1 when data were missing. In this analysis, the estimated 1-year rate for development/progression of peripheral neuropathy was greater in patients in the eribulin group (21.4%) than in the TPC group (9.5%), and the corresponding figures for the estimated 2-year rates were 23.1% and 9.5%. In the BCP group, there were 288 (34.8%) patients with any treatment emergent peripheral neuropathy, and resolution at the time of follow-up after last treatment had occurred in only 14.2% (n=41) with a median time to resolution of 8.1 weeks. In this patient population the median time to onset of peripheral neuropathy was 23.4 weeks. In a sub-group analysis in the pooled BCP group, the incidence of neuropathy related to eribulin treatment was similar in patients without pre-existing neuropathy, with Grade 1 pre-existing neuropathy, and with Grade ≥ 2 pre-existing neuropathy (31.5% [197/625], 34.5% [49/142], and 29.6% [8/27], respectively).

The risk of infections and infestations (any) were more common in the eribulin group (41.9%, n=211) than in the TPC group (26.3%, n=TPC). This most likely reflects the higher incidence of neutropenia in the eribulin group compared with the TPC group. Infection/infestations (preferred terms) which occurred with a frequency of ≥ 2.0% in the eribulin and more commonly than in the TPC group were: urinary tract infection (9.7%, n=49 vs 5.3%, n=13); nasopharyngitis (4.8%, n=24 vs 2.8%, n=7); upper respiratory tract infection (5.2%, n=26 vs 2.0%, n=5); rhinitis (4.4%, n=22 vs 1.2%, n=3); influenza (4.4%, n=22 vs 0.8%, n=2); cystitis (2.4%, n=12 vs 1.2%, n=3); pharyngitis (2.4%, n=12 vs 0.4%, n=1); bronchitis (2.2%, n=11 vs 0.8%, n=2); and sinusitis (2.2%, n=11 vs 0.8%, n=2). Infections/infestations leading to discontinuation in the eribulin group occurred in 5 (1.0%) patients (2 x pneumonia, 1x lung infection, 1 x pelonephritis, 1 x septic chock) and in 1 (0.4%) patient in the TPC group (aspergillosis).

The risk of cardiovascular AEs occurred more commonly in patients in the eribulin group than in the TPC group: cardiac disorders 6.6%, n=33 vs 4.0%, n=33, respectively; and vascular disorders 16.3%, n=92 vs 13.0%, n=32, respectively). Both tachycardia and palpitations occurred more frequently in the eribulin group than in the TPC group: tachycardia 3.6%, n=18 vs 1.2%, n=3, respectively, and palpitations 1.6%, n=8 vs 0.4%, n=1, respectively. Arrhythmia was reported in 1 (0.2%) patient in the eribulin group and 1 (0.4%) patient in the TPC group, and atrial fibrillation and atrial tachycardia were both reported in 1 (0.2%) patient in the eribulin group and no patients in the TPC group. There were no reports of Torsade de pointes in either treatment group. There were 3 patients with treatment-emergent serious AEs in the eribulin group (2 x pericardial effusion, 1 x cardiac failure) compared with no patients in the TPC group. There were no patients in either treatment group with cardiac disorders leading to discontinuation.

In the eribulin group (vs the TPC) group, there were higher incidences of hypertension (3.6%, n=18 vs 1.6%, n=4), hot flush (2.8%, n=14 vs 2.0%, n=5), and hypotension (2.6%, n=13 vs 1.6%, n=4). There were 2 (0.4%) patients with deep vein thrombosis in the eribulin group compared with 3 (1.2%) in the TPC group, and the respective figures for embolism were 1 (0.2%) and 2 (0.8%) patients. Discontinuations due to vascular disorders were reported in 1 (0.2%) patient in the eribulin group (1 x deep vein thrombosis) and no patients in the TPC group. Fatal treatment-emergent vascular disorders (any term) were reported in 1 (0.2%) patient in the eribulin group (cardiovascular insufficiency) and 2 patients in the TPC group (1 x cardiovascular insufficiency;1 x embolism).

Skin and subcutaneous tissue disorders (any) occurred more frequently in patients in the eribulin group (52.9%, n=266) compared with the TPC group (32.0%, n=79), due primarily to the greater number of patients with alopecia. However, palmar plantar erythrodysaesthesia syndrome occurred notably more frequently in patients in the TPC group (5.7%, n=14) than in patients in the eribulin group (1.4%, n=7).

There does not appear to be an increased risk of hepatic, renal or immune system toxicity associated with eribulin compared with TPC.

9.3. First round assessment of benefit-risk balance

It is considered that the benefit-risk balance for eribulin, given the proposed usage, hinges on whether the small, but clinically meaningful and statistically significant OS benefit of 2.7 months [95% CI: 1.0, 4.5] (updated analysis, pivotal study) observed with eribulin compared with TPC outweighs the increased risks of eribulin compared with TPC (in particular neutropenia and peripheral neuropathy).

On balance, it is considered that the benefit-risk balance is marginally favourable for eribulin, given the proposed usage. The OS benefit observed with eribulin is small, but clinically meaningful for the proposed patient population for whom other treatment options are limited

and appear to offer no OS benefit. The risks of eribulin treatment are similar in type to those known to be associated with other chemotherapy agents used to treat advanced metastatic breast cancer. The risks appear to be manageable by dose delays, dose reductions, and symptomatic therapy rather than treatment discontinuation. The risk-benefit balance can only be considered to be favourable in patients with a life expectancy of at least 3 months as this was an inclusion.

10. First round recommendation regarding authorisation

- It is recommended that eribulin be approved as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.
- It is recommended that the proposed eribulin treatment regimen for the proposed indication be approved.

11. Clinical questions

11.1. Pharmacokinetics

1. In a public document, the sponsor has stated that "the geometric mean dose-normalized systemic exposure increased two-fold compared to patients with normal renal function. A lower starting dose of 1.1 mg/m^2 is recommended for patients with moderate renal impairment" [Eisai FDA Advisory Subcommittee Briefing Document; October 25, 2010]. However, the data supporting this statement relating to the "two-fold" increase could not be located in the submission. Please provide the data supporting the statement.

11.2. Efficacy

1. Why was prior chemotherapy with capecitabine not a specific inclusion criteria for the pivotal Phase III study 305, although it had been for the Phase II study 211 ?
2. In the pivotal study [305], are the two patients in the eribulin group listed as having Stage 0 breast cancer at diagnosis those with identification numbers [redacted information] in Listing 16.2.4.4 ? Did these 2 patients have Stage 0 breast cancer, and if so why were they included in the study?
3. In the protocol (pivotal study 305), it was stated that patients in the OS analysis were to censored at the date last known to be alive, but in the OS analysis provided in the CSR (pivotal study 305) patients were censored at the data cut-off date (i.e., 12 May 2009). Why was the OS censoring rule used in the CSR changed from that specified in the protocol, and did the different censoring rules influence the results of the provided OS analysis?
4. In the CSR (pivotal study 305), it is stated that "in addition to the PFS analyses as detailed in the SAP, following unblinding, discussion surrounding the interpretation of the "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" led to the formulation of a new set of PFS rules for censoring/progression. As such, this approach represents a *post hoc analysis*, as the methods used to define and interpret the results were not part of the pre-specified analysis. This analysis is based upon the Independent review of the radiological assessments.....The main difference from this analysis as opposed to the PFS detailed in the SAP is that it takes into account

progressions from non-target lesions (i.e., unequivocal progressions) in addition to new lesion and target lesion progression events". The sponsor is requested to respond to the following questions related to this matter.

- Were FDA (and/or EMEA) officials participants in the "discussion" in addition to representatives of the sponsor ?
- If representatives of the FDA (and/or EMEA) were present, were the changes to the PFS censoring/progression rules after unblinding of the data driven primarily by regulatory officials ?
- What were the specific issues relating to interpretation of the "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" which resulted in the changes to the censoring/progression rules for the PFS?
- Did the results for PFS differ for the analysis using the *post hoc* censoring/progression rules and the analysis using the protocol specified censoring/progression rules?

11.3. Safety

No questions

12. Second round evaluation of clinical data submitted in response to questions

This second round clinical evaluation report provides comments on the sponsor's responses to the clinical questions (Section 11, above) raised following the first round clinical evaluation; the second round benefit-risk assessment; the second round recommendation regarding authorization; and second round comments on the product documentation.[11] The first and second round clinical evaluation reports have been prepared by the same clinical evaluator. The two reports are complementary and should be considered together.

12.1. Clinical Pharmacokinetics

12.1.1. Sponsor's response to Question 1:

The sponsor provided the source of the relevant data. In addition to the data provided in the text of these responses, the sponsor also provided individual patient information relating to the renal impairment status and dose-normalized AUC results for each patient from the relevant 6, Phase 1 studies identified in the responses.

12.1.2. Clinical evaluator's comment:

The sponsor has satisfactorily identified and summarized the source data supporting the statement that geometric mean dose-normalized systemic exposure was two-fold higher in patients with moderate renal impairment compared with subjects with normal renal function. The implications of the data are discussed in the section on Product Information.[12]

[11] Details of PI comments are not included in this CER Extract.
[12] Not part of this Extract.

12.2. Clinical Efficacy

12.2.1. Sponsor's response to Question 1:

Study 211 required having prior chemotherapy with capecitabine, and Study 305 did not. Prior capecitabine therapy was not mandated in study 305 but was not excluded. To ensure balance across treatment arms, it was included as a randomization stratification factor. The subgroup analysis of study 305 showed a benefit for eribulin in both capecitabine pretreated and naïve subgroups. This was discussed with EMA prior to study start. EMA's position was if results were consistent between the subgroups of patients treated and not previously with capecitabine in Study 305 and consistent with the 211 results, then 211 would be supportive of the 305 study.

12.2.2. Clinical evaluator's comment

No explanation has been provided for why the sponsor decided not to specify prior treatment with capecitabine as an inclusion criterion for the pivotal study. The clinical issues relating to the sub-group analyses of overall survival and progression-free-survival in capecitabine-pretreated and capecitabine-naïve patients in the pivotal study has been discussed in the first round clinical evaluation report. Furthermore, the results of the sub-group analyses in capecitabine-pretreated and capecitabine-naïve patients are also discussed above.

12.2.3. Sponsor's response to Question 2:

Patients [redacted information] and [redacted information] were initially diagnosed with stage 0 however at study entry both patients were locally advanced or had metastatic disease.

Patient [redacted information] was stage IIa at initial diagnoses. In [redacted information] the patient had recurrence of disease and reassessed to locally advanced/ metastatic disease and received multiple lines of therapy (6), in [redacted information] (study entry) patient was stage IV.

Patient [redacted information] was diagnosed in [redacted information] with ductal adenocarcinoma of the breast Stage 0. Approximately in [redacted information] she was diagnosed with locally advance/metastatic carcinoma and received multiple lines (4) of chemotherapy before she was selected to participate in this study.

Patient [redacted information] was diagnosed in [redacted information] with ductal adenocarcinoma of the breast Stage 0. Approximately in [redacted information] she was diagnosed with locally advance/metastatic carcinoma and received multiple lines (4) of chemotherapy before she was selected to participate in this study.

12.2.4. Clinical evaluator's comment:

The sponsor's response is satisfactory.

12.2.5. Sponsor's response to Question 3:

Within two weeks of the data cut-off date (12 May 2009), the sponsor followed up the status of all study subjects who were known to be still remaining in the study (not dead, not lost to follow up, not withdrawn consent), and confirmed whether the subject was alive on 12 May 2009 or if the subject had died, the date last known to be alive, was included in the clinical database. If the subject was alive on 12 May 2009, we censored the subject in OS analysis. This approach is in agreement with the plan outlined in the protocol. The protocol stated that patients in the OS analysis were censored at the date last known to be alive.

12.2.6. Clinical evaluator's comment:

The sponsor's response is satisfactory.

12.2.7. Sponsor's response to Question 4:

The primary analysis of PFS was done according to the Statistical analysis plan using the censoring rules in the SAP. Additional PFS calculations were done as sensitivity analysis using different censoring rules including when death or progression occurred after two or more missed assessments. This analysis was based on a recommendation from FDA in the pre-meeting minutes from our EOP II meeting received on 21-March 2008. Additional analysis using the FDA guidance and the Clinical Trials Endpoint guidance were also done, without advice from FDA or EMA. Results were similar in all analyses, however statistical significance was lost in those analysis where censoring was more extensive. The Censoring rules for the primary analysis are listed (below in Table 38).

Table 38: Censoring rules for progression free survival based on independent review data.

Situation	End Date	Censored
Documented PD during the study	Date of the first assessment of the series of the tests that determined PD	No[a]
Death during the study before PD	Date of death	No[a]
Discontinued due to PD, but no documented PD	Date of last tumour assessment before discontinuation	Yes
Discontinued due to clinical progression per investigator	Date of last tumour assessment before discontinuation	Yes
No baseline assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death, and no post-baseline tumour assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death with post-baseline tumour assessments	Date of last tumour assessment	Yes
New anticancer treatment started prior to disease progression	Date of last tumour assessment before start of new treatment	Yes
Death or PD after one or more missed tumor assessments	Date of the last assessment before missed assessments	No[a]
Patients still on treatment without PD as of data cut-off	Date of last tumour assessment	Yes

a - Earliest date among the three dates is used in calculating the progression free survival.

The censoring according to FDA guidance is listed in Table 39.

Table 39: PFS using FDA guidance document: sensitivity analysis.

Situation	End Date	Censored
Documented PD during the study	Earliest of • Date of radiological assessment showing new lesion (if progression is based on new lesion); • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	No[a]
Death during the study before PD	Date of death	No[a]
Discontinued due to PD, but no documented PD	Date of last tumour assessment before discontinuation	Yes
Discontinued due to clinical progression per investigator	Date of last tumour assessment before discontinuation	Yes
No baseline assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death, and no post-baseline tumour assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death with post-baseline tumour assessments	Date of last tumour assessment	Yes
New anticancer treatment started prior to disease progression	Date of last tumour assessment before start of new treatment	Yes
Death or PD after two or more missed tumor assessments	Date of the last assessment before missed assessments	Yes
Patients still on treatment without PD as of data cut-off	Date of last tumour assessment	Yes

The estimated HRs for PFS range from 0.819 to 0.868 (see Table 40, below) which is similar to the planned analysis (HR=0.865, 95% CI = (0.714, 1.048), (see Table 41, below).

Table 40: Progression free survival forest plot of hazard ratio – independent review summary; ITT population.

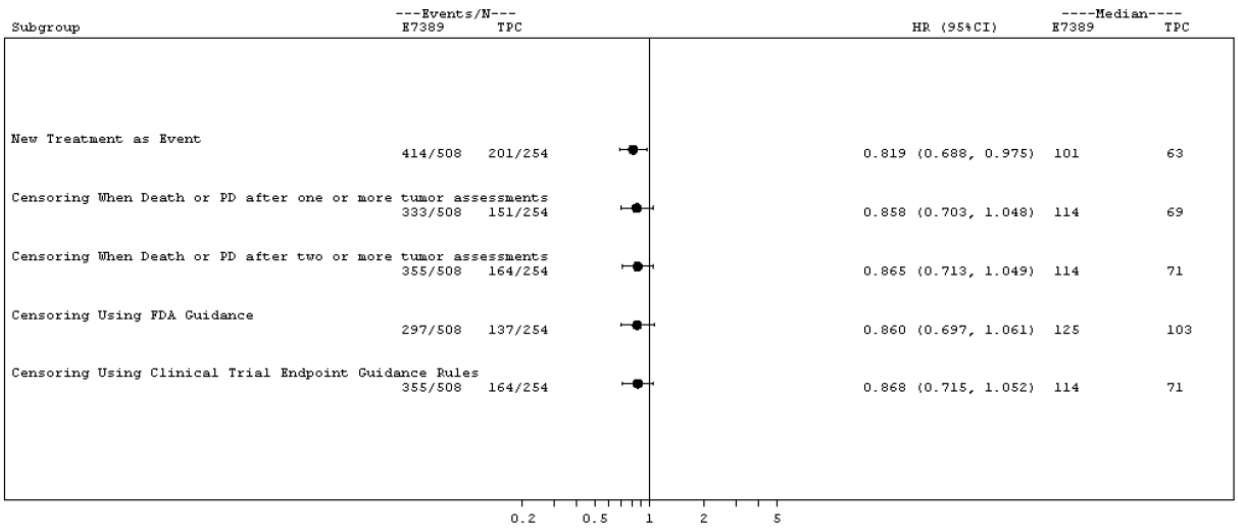


Table 41: Progression free survival – independent review summary; ITT population.

		Treatment Group	
		E7389 (N=508)	TPC (N=254)
Number of patients	Progressed or died	357 (70.3%)	164 (64.6%)
	Censored	151 (29.7%)	90 (35.4%)
Kaplan-Meier estimate of PFS (days)	1st Quartile (95% CI)	57.0 (55.0, 58.0)	54.0 (49.0, 57.0)
	Median (95% CI)	113.0 (101.0, 118.0)	68.0 (63.0, 103.0)
	3rd Quartile (95% CI)	187.0 (174.0, 205.0)	194.0 (147.0, 239.0)
Stratified log-rank test	p-value	0.137	
Hazard Ratio (E7389/TPC)*	Estimate	0.865	
	95% CI	(0.714, 1.048)	
Kaplan-Meier estimate of PFS at 3 months	3-month PFS rate (95% CI)	0.571 (0.526, 0.617)	0.449 (0.381, 0.517)
Kaplan-Meier estimate of PFS at 6 months	6-month PFS rate (95% CI)	0.263 (0.219, 0.307)	0.276 (0.210, 0.342)
Kaplan-Meier estimate of PFS at 9 months	9-month PFS rate (95% CI)	0.123 (0.085, 0.161)	0.113 (0.054, 0.172)
Kaplan-Meier estimate of PFS at 12 months	12-month PFS rate (95% CI)	0.088 (0.051, 0.125)	0.073 (0.020, 0.126)

Source: Listing 16.2.6.1.2 and Statistical Analysis Appendix 3.1
Note: * Hazard ratio based on a Cox model including HER2/neu status, prior capecitabine treatment and geographical region as strata.
Note: NE = Not Estimable due to insufficient events.

12.2.8. Clinical evaluator's comment:

The sponsor's response is acceptable. The primary analysis of the PFS was by Independent Review (HR = 0.865 [95% CI: 0.714, 1.048]; p=0.137) (see Table 4, above). PFS was defined as the time from randomization until progressive disease or death due to any cause. PFS was censored for patients who did not have an event (i.e., those who were lost to follow-up or who had not progressed at the date of data cut-off). The primary analysis of PFS was based on the Independent review of tumor assessment in the ITT population, with the date of objective disease progression being based on the date of radiological disease progression as assessed by the Independent review of imaging data using RECIST criteria. Patients without disease progression were censored on the date of their last radiological assessment preceding the start of any additional anti-cancer therapy. Patients were also censored if they discontinued

randomized treatment and began any alternative anti-cancer therapy prior to disease progression. The result of the primary PFS analysis was generally consistent with the results of the sensitivity analyses based on different censoring rules.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefit

No new clinical information was submitted in response to the clinical questions. Accordingly the benefits of eribulin for the proposed indication are unchanged from those identified in the initial (first round) clinical evaluation report (above).

13.2. Second round assessment of risks

No new clinical information was submitted in response to the clinical questions. Accordingly the risks of eribulin for the proposed indication are unchanged from those identified in the initial (first round) clinical evaluation report (above).

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of eribulin for the proposed indication remains favourable.

14. Second round recommendation regarding authorisation

- It is recommended that eribulin be approved as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.
- It is recommended that the proposed eribulin treatment regimen for the proposed indication be approved, but with a downward dose adjustment for patients with moderate renal impairment.

15. References

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16. Appendix: Additional material relevant to the evaluation

16.1. Response Evaluation Criteria in Solid Tumours (RECIST) Quick Reference (reproduced from Study 305, Protocol, Appendix 8)

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

  Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

  Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

  Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement –

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be target lesions selected for response assessment. Conventional CT and MRI should be should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

16.2. Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

16.3. Response Criteria

16.3.1. Evaluation of target lesions

*Complete Response (CR): Disappearance of all target lesions

* Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD

*Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

* Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

16.3.2. Evaluation of non-target lesions

*Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

*Incomplete Response/ Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

*Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1.)

1. Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

16.3.3. Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements

recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

16.3.4. Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

16.3.5. Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

16.3.6. Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

16.3.7. Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

16.3.8. Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g. early death due to other reasons, early discontinuation of treatment, major protocol violations, etc). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

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