EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/514195/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report
For
Halaven
eribulin

Procedure No. EMEA/H/C/002084

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

1A9PTX10	Human ovarian cancer cell line (paclitaxel resistant)
1A9PTX22	Human ovarian cancer cell line (paclitaxel-resistant)
AE	Adverse event
AETP	All eribulin treated patients
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BCP	Breast cancer patients
BSA	Body surface area
BUN	Blood urea nitrogen
CFC-GEMM	Colony forming cell-granulocyte, erythrocyte, macrophage, megakaryocyte
CFU-GM	Colony forming unit-granulocyte, macrophage
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum observed concentration
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CT	Chemotherapy regimens
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DoR	Duration of Response
E7389	Eribulin mesylate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
GC	Gas chromatography
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GD	Gestation days
GLP	Good Laboratory Practice
HALO	Hematotoxicity Assay via Luminescence Output
HER2/neu	Human epidermal growth factor receptor 2
hERG	Human ether a-go-go related gene
HPLC	High performance liquid chromatography
HR	Hazard ratio
IC	Ion chromatography
IC50	Half-maximal inhibitory concentration
IC90	Inhibitory concentration 90%
IR	Infrared Spectroscopy
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice recognition system
LLDPE	Linear low density polyethylene
LRBC	Locally recurrent breast cancer
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MS	Mass spectrometry
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National Cancer Institute
NOAEL	No-Observed-Adverse-Effect Level
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival

PD	Progressive disease
PFS	Progression-Free Survival
P-gp	Permeability glycoprotein
PO	Per os
PP	Per protocol
PR	Partial response
PTFE	Polytetrafluoroethylene
Pts	Patients
Q2D×3	Every other day for 3 injections with a two-day rest between weekly cycles (Monday-Wednesday-Friday schedule)
Q4D×3	Once every four days for a total of 3 injections
Q7D×3	Once a week for 3 weeks
RBC	Red blood cell
RECIST	Response Evaluation Criteria In Solid Tumours
RET	Reticulocyte
RMP	Risk management plan
S9	Liver metabolic activation system, designates a supernatant from centrifugation at 9000×g, used for metabolic activation tests
SAE	Serious adverse event
SD	Stable disease
SEG	Neutrophil
SmPC	Summary of product characteristics
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TPC	Treatment of Physician's Choice
UK	United Kingdom
ULN	Upper limit of normal
UV	Ultraviolet spectroscopy
WBC	White blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eisai Europe Ltd. submitted on 30 March 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Halaven, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 May 2009.

The applicant applied for the following indication:

HALAVEN monotherapy is indicated for the treatment of patients with breast cancer who have received at least two chemotherapeutic regimens for locally advanced or metastatic disease.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/47/2008 for the following condition(s):

Treatment of breast carcinoma.

on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 14 December 2005, 28 June 2006 and 22 January 2009. The Scientific Advices pertained to quality and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

A new application was filed in the following countries: Switzerland on 26 May 2009 and Singapore on 26 May 2009.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Tomas Salmonson** Co-Rapporteur: **Jens Ersbøll**

- The application was received by the EMA on 30 March 2010.
- The procedure started on 26 May 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 28 July 2010 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 August 2010.
- During the meeting on 20-23 September 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 November 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 December 2010.
- During the meeting on 20 January 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Halaven on 20 January 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 January 2011.

2. Scientific discussion

2.1. Introduction

Breast cancer is the most frequent cancer in women worldwide with an estimated 1.38 million new cases in 2008, constituting 23% of all cancers in women. Approximately 1 in 8 women will develop breast cancer in their lifetime. While a small proportion of patients have advanced disease at diagnosis, around one third will eventually have metastatic disease, for which there is still no cure. Palliative treatment with radiotherapy, chemotherapy, hormonal and biologic therapy, can however reduce tumour symptoms and/or prolong life.

Eribulin mesylate is a structurally simplified synthetic analogue of halichondrin B, which is a natural product isolated from the marine sponge *Halichondria okadai*. Eribulin inhibits the growth phase of microtubule dynamics and sequesters tubulin into non-productive aggregates. This pattern is distinct from that of members of tubulin-targeting classes currently in clinical use, including taxanes, vinca alkaloids, and epothilones. Eribulin has shown *in vitro* activity against drug-resistant cells that harbour β-tubulin mutations associated with taxane resistance.

Three CHMP scientific advices were sought and given during the development process:

The first, dated December 14, 2005, concerned the Phase-II Study 211. The CHMP believed that a non-controlled phase-II study was unlikely to provide sufficient information for registration of eribulin, and recommended a comparative phase-III confirmatory trial. The CHMP also recommended that a comparator arm be included in Study 211. This was not done.

The second scientific advice, dated June 28, 2006, mainly concerned the Phase-III Study 305, pivotal for the present application. The CHMP did not agree with the applicant's proposal to use progression-free survival (PFS) as primary endpoint, and stated that overall survival (OS) is the preferred primary endpoint. Furthermore, the PFS analysis must be consistent with the primary analysis.

The CHMP agreed that a phase-II study and one pivotal phase-III study that included a control arm of Treatment of Physician's Choice could fulfil the requirements for a MAA in this setting. The inclusion criteria differed with regard to requirement of prior capecitabine therapy (yes in Study 211, no in Study 305). The CHMP stated that if the results are similar in the whole population of Study 305, in its subset previously treated with capecitabine, and in Study 211, this homogeneity will support the results of Study 305. However, if a benefit is limited to patients previously treated with capecitabine (in Study 211 and the subset of Study 305), one could consider that eribulin is beneficial only in this subset or when it is compared with a regimen that does not include capecitabine. In addition, previous use of capecitabine should be a stratification factor in Study 305. In conclusion, the CHMP could consider the results of Study 211 as supportive for the intended application provided that the benefit is similar in patients having received capecitabine or not before trials.

The third scientific advice dated January 22, 2009, concerned the applicant's proposal for the regulatory starting materials for the synthesis of eribulin mesylate active substance. The CHMP agreed that it was acceptable to use ER-803895-00 and ER-804028-00 as starting materials.

The indication applied for initially was the following:

- HALAVEN monotherapy is indicated for the treatment of patients with breast cancer who have received at least two chemotherapeutic regimens for locally advanced or metastatic disease (see section 5.1).

The finally approved indication is as follows:

- HALAVEN monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease (see section 5.1). Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

2.2. Quality aspects

2.2.1. Introduction

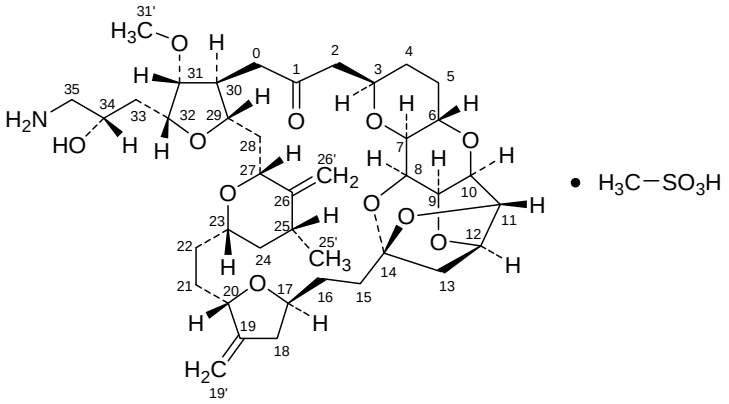
Halaven 0.44 mg/ml solution for injection is formulated as a 2ml clear colourless aqueous solution. Each vial contains 0.88 mg of eribulin (in the form of 1 mg eribulin mesylate) in 2 ml solution. The active substance is a synthetic analogue of halichondrin B (a natural product isolated from a marine sponge). The excipients used are all common compendial excipients: ethanol anhydrous, hydrochloric acid, sodium hydroxide, water for injection.

The product is to be marketed in a clear glass vial (EP Type I glass) with a teflon coated butyl rubber stopper and an aluminium seal.

2.2.2. Active Substance

(2R, 3R, 3aS, 7R, 8aS, 9S, 10aR, 11S, 12R, 13aR, 13bS, 15S, 18S, 21S, 24S, 26R, 28R, 29aS)-2-[(2S)-3-Amino-2-hydroxypropyl]-3-methoxy-26-methyl-20,27-dimethylidenehexacosahydro-11,15:18,21:24,28-triepoxy-7,9-ethano-12,15-methano-9H,15H-furo[3,2-i]furo[2',3':5,6]pyrano[4,3-b][1,4]dioxacyclopentacosin-5(4H)-one methanesulfonate (salt)

Its structure is provided below



- H_3C-SO_3H

Manufacture

The detailed description of the manufacturing process for eribulin mesylate is provided. The synthesis is described in detail (raw materials, amounts, conditions and controls) along with a process flow diagram. Eribulin mesylate active substance is isolated as an amorphous compound.

Eribulin mesylate is synthesised in 8 steps starting from 2 starting materials. These starting materials have been accepted as the starting point by the Scientific Advice procedure EMEA/CHMP/SAWP/19821/2009 procedure no. EMEA/H/SA/641/2/2008/I. It was agreed that the

proposed starting point of a long synthesis, was suitable based on *e.g.* that the proposed starting materials are well characterised and their impurity profiles under control.

The manufacturing process of the active substance has been sufficiently described. Specifications are provided for each reagent and solvent used in the manufacture of eribulin mesylate, however there were additional information needed for the specifications of the reagents and materials, the manufacture and the specifications and this will be provided in the Follow-up Measures (see the list of FUMs). Adequate method descriptions and validation summary have been presented.

The commercial synthesis of eribulin mesylate will be carried out at the authorised manufacturer. Data are provided on three full scale batches. The process operating ranges and the actual operating conditions are satisfactory and provided for each process step. Batch data produced with the proposed synthetic route show that the active substance can be manufactured reproducibly.

The proof of chemical structure, potential isomerism and physicochemical properties including: description (white powder), solubility, partition coefficient, dissociation constant, specific rotation, thermal analysis, hygroscopicity (the product is hygroscopic), stability in solution, polymorphism (eribulin mesylate exists as an amorphous solid and no polymorphism is observed) of eribulin mesylate have been confirmed by using the following techniques: Ion chromatography (IC), Ultraviolet Spectroscopy (UV), Infrared Spectroscopy (IR), Mass Spectrometry (MS), Nuclear Magnetic Resonance Spectroscopy (NMR), Single-Crystal X-ray Crystallography, Circular Dichroic Spectroscopy and Potential isomerism.

Specification

The specification for eribulin mesylate includes the following tests: appearance (visual), identification (IR), related substances by High-Performance Liquid Chromatography (HPLC), assay (HPLC), water content (Karl Fischer), methanesulfonic content (IC), specific rotation (polarimetry), residual solvents by Gas chromatography (GC), residual metals (ICP-AES).

Satisfactory descriptions are provided for the analytical procedures and validation data are provided for each of the methods in line with ICH requirements. Copies of representative chromatograms are provided.

The specification includes: process impurities, stereochemical isomers, degradation products, residual solvents, and residual metals. A complete analysis for the origin, fate and control of impurities during the manufacturing process is provided. Impurities levels are justified by toxicological qualification limits or controlled to not more than 0.10%.

Batch analysis are presented for 18 batches (including 5 commercial batches) manufactured between 2000 and 2008. Data are consistent between batches and comply with the proposed specification.

Eribulin mesylate is packaged in a polytetrafluoroethylene (PTFE) bottle with a PTFE screw cap equipped with an o-ring (fluorinated rubber coated with tetrafluoroethylene-perfluoroalkylvinyl ether copolymer: PFA). Appropriate specification (including appearance, identification, dimensions) is provided along with a drawing of the bottle.

The secondary container, is a laminated aluminium bag consisting of linear low density polyethylene (LLDPE) film (inner), nylon film, aluminium foil and polyester film (outer).

Stability

Primary stability studies on pilot scale batches

Stability results have been presented for 3 pilot scale batches kept in the commercial packaging. Batches have been stored 24 months under long term conditions (-65°C and -20°C), 12 months under intermediate conditions (5°C) and, 1 month under "short time excursion condition", (25°C/60%RH). The stability protocol is in accordance with ICH recommendations Q1A (R2). The parameters tested against the final specification were: Appearance, identification, assay, impurities, water content and residual solvents.

For batches stored at -65 °C up to 24 months no significant changes are observed for any parameters studied but under the other conditions, the active substance was found unstable.

Confirmatory studies on production scale batches

Data up to 24 months under long term conditions, 12 months under intermediate conditions are provided for 3 production scale batches. The protocol, analytical procedures, specifications and packaging used are identical to those of the primary stability study. Data confirmed the results from the primary stability batches, the product is only stable at -65 °C.

Forced degradation studies

Testing was performed under a variety of stress conditions such as light exposure, heat and humidity.

Photo stability testing was performed in accordance with the ICH guidance Q1B

Solid state stress tests by heat and humidity were conducted at 60 °C and 30 °C/75% RH for 1 month. The active substance was unstable when exposed to light, heat and humidity.

Based on the stability studies performed, a re-test period of 2 years for eribulin mesylate for storage at -65 °C kept in its commercial packaging is considered acceptable.

In accordance with EU GMP guidelines [1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The pharmaceutical development has been adequately conducted and can be summarised below.

The key properties of eribulin mesylate active substance such as solubility and stability in aqueous solution are discussed appropriately in the dossier. An important parameter for the performance of the drug product is the solubility of the active substance. There should be no solubility problems at the desired concentration of 0.44 mg/ml. Compatibility with regard to excipients is demonstrated and confirmed by stability data of the drug product in aqueous ethanol solution.

The function of excipients is detailed. Ethanol anhydrous and water (WFI) are used as solvent. Ethanol anhydrous is used to facilitate the dissolution and safe handling of eribulin mesylate during the drug product manufacturing since it is readily dissolved in ethanol at room temperature. Hydrochloric acid and/or sodium hydroxide are used to adjust pH if needed.

The final commercial formulation is the same as the one used for the clinical studies apart for that the amount per vial was changed during development from 0.44 mg to 0.88 mg by increasing the fill

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

volume from 1 ml to 2 ml. A provision to add HCl or NaOH for pH adjustment was added for the manufacture based on the understanding of the pH dependent stability.

No overage is used during manufacture but an overfill of the vials is specified. A fill volume overage of 0.26 ml per vial is used to ensure that the labelled vial content of eribulin (0.88 mg/2 ml) can be withdrawn.

Physico-chemical properties such as density and pH have been adequately studied. To conclude Eribulin mesylate was found to be physically and chemically stable in aqueous solutions over a pH range of 5-9.

Halaven 0.44 mg/ml solution for injection is manufactured by a conventional aseptic process for sterile liquid since eribulin mesylate cannot withstand terminal steam sterilization. The manufacturing process has not changed much over time. The manufacturing parameters and their optimisation are satisfactorily described. The changes performed (change of scale and a provision to adjust the pH) have no impact on the performance of the drug product.

Stability studies have shown that eribulin mesylate in aqueous solution is not sensitive to light. Therefore, no precautions relative to light protection are required during the manufacturing process.

The choice of the container closure system for eribulin mesylate solution for injection has been fully justified. It consists of a clear glass vial, an elastomeric closure, and an aluminium seal. Adequate compatibility studies (including leachage and extractable studies) and stability studies have confirmed that the selected container was appropriate.

The finished product is a sterile and non-pyrogenic drug product. In order to demonstrate that the container closure system prevents microbiological contamination, a microbial challenge study was performed. No growth occurred indicating the container closure was appropriate for preventing microbiological growth. Container closure integrity has also been demonstrated through annual sterility testing of stability samples. No sterility failures have been found in the stability studies.

The product was evaluated for stability and compatibility in common diluents and equipment used for infusion. The diluents evaluated were D5W (5% (w/v) aqueous solution of dextrose) and normal saline (0.9% (w/v) aqueous solution of sodium chloride). The conclusion is that D5W is not recommended as a diluent. Compatibility was also demonstrated with different equipments i.e.: syringes (polypropylene PP) and intravenous bags (polypropylene and polyethylene or polyolefin with polyvinylchloride/diethylhexyl phthalate ports).

No compatibility studies have been performed with other medicinal products

Adventitious agents

There is no risk identified since none of the excipients in Halaven 0.44 mg/ml solution for injection is of human or animal origin.

Manufacture of the product

Halaven 0.44 mg/ml solution for injection is manufactured using a conventional aseptic process for sterile liquid products packaged in glass vials that cannot withstand terminal steam sterilisation.

The manufacturing process is described in sufficient detail as well as flow-chart provided. In-process controls are defined. The process cover **(I)** Compounding of ingredients, **(II)** Filtration (pre-filtration through 0.45µm followed by two 0.22 µm filters in series) into a stainless steel tank, **(III)** Filling into vials and **(IV)** Inspection of vials. Adequate in process controls and control of the critical steps are included.

Data from three commercial scale batches manufactured are included. The validation of the process is satisfactory.

All excipients are tested for compliance to their corresponding monographs in the European Pharmacopoeia. The methods used are those from the Ph.Eur. and no further validation was deemed necessary.

Product specification

The release and end of shelf life specification for Halaven 0.44 mg/ml solution for injection include the following parameters: appearance/foreign insoluble matter (visual), identification (IR and HPLC), particulate matter (Ph.Eur.), fill volume (Ph.Eur.), pH (potentiometry), assay (HPLC), related substances (HPLC), sterility (Ph. Eur.), endotoxins (Ph.Eur.). The specifications have been justified and are considered satisfactory. Satisfactory descriptions and methods validations are provided for the analytical procedures.

Batch analysis data are provided for 21 batches of eribulin 0.44 mg/ml solution for injection. All the results meet the proposed specification. Impurities levels were found acceptable and were toxicologically qualified.

The container closure system for Halaven 0.44 mg/ml solution for injection consists of the following parts: a 5 ml clear glass Type I glass (borosilicate glass with ammonium sulphate treatment) vial, a 13 mm teflon coated butyl rubber elastomeric closure and a 13 mm flip-off blue aluminium seal (not in contact with the product). Adequate specifications are provided along with technical drawings of the vial, stopper and seal. The secondary packaging component is a carton box for each vial. Specifications and drawings of the packaging components are enclosed. The vials comply with the Ph. Eur. Monograph 3.2.1 Glass containers for pharmaceutical use.

Rubber stoppers comply with the Ph. Eur. monograph 3.2.9 Rubber closures for containers for aqueous parenteral preparations, for powders and freeze-dried powders.

Stability of the product

Primary stability studies

Data are provided for 3 pilot scale batches kept in the commercial packaging stored for 36 months at 25°C/60%RH, 12 months at 30°C/65%RH and 6 months at 40°C/75%RH under ICH conditions. Parameters investigated are: Appearance, particulate matter, pH, assay, impurities and sterility (initial and then annually)

The batches are manufactured according to the current process at the site intended for commercial production. The vials have been stored in both the upright and the inverted position.

The stability data show that the degradation level increases with temperature but the results remain within the specifications under all tested conditions. There is no clear difference between samples stored upright or inverted.

Photo stability study

Data are provided for one batch exposed to light conditions according to ICH Q1B (Option 1). The vials have been stored in the upright, inverted and the horizontal orientation respectively.

From studies of light exposure as well as thermal cycling it may be concluded that there is no major change observed.

Thermal cycling stability study

Data are provided for one batch exposed to three cycles of alternating exposure to frozen (-25 to -10°C) and accelerated (40 °C/75% RH) storage conditions. The vials have been stored in both the upright and the inverted orientation. As expected considering the fact that the degradation has been demonstrated to be temperature dependent (see results from primary stability studies) a slightly more pronounced degradation in terms of increase in levels of degradation products and slight decrease in assay is seen.

In-use shelf-life

For undiluted drug product stored in syringes, it can be assigned an in-use shelf-life of no more than 4 hours at 25 °C or no more than 24 hours at 2 to 8 °C.

For diluted solution, the in-use shelf life should be not more than 24 hours at 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions and in this case the responsibility is on the user.

Based on the stability data, the proposed shelf-life and storage conditions for the drug product packaged in the commercial packaging as stated in the summary of product characteristics (SmPC) can be accepted.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In general satisfactory documentation has been provided to confirm the acceptable quality of this medicinal product, and no major objections have been raised during evaluation. The active substance a new chemical entity, a synthetic analogue of halochondrin (natural product isolated from a marine sponge) has been adequately characterized and the specification is acceptable in view of the route of synthesis and the various ICH guidelines.

Concerning the finished product the complete control strategy and an established manufacturing process guarantees consistent control of the product quality which should have a satisfactory and uniform performance in the clinic. The drug product is stable with respect to degradation.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant provided a letter of undertaking and committed to resolve these as Follow-Up Measures after the opinion within an agreed timeframe.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

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2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development of eribulin mesylate consisted in pharmacology, pharmacokinetics and toxicity studies including the evaluation of the genotoxicity and reproductive toxicity. Primary pharmacology studies were conducted in mice. Pharmacokinetics studies were conducted in mice, rats and dogs. Safety pharmacology and toxicology studies were conducted in rats and dogs. Eribulin mesylate was generally administered intravenously, similarly to the clinical route of administration.

According to the applicant, all pivotal toxicology studies and the majority of safety pharmacology studies have been performed in accordance with Good laboratory practices (GLP).

2.3.2. Pharmacology

Primary pharmacodynamic studies

A series of *in vitro* and *in vivo* studies have been conducted to evaluate the primary pharmacodynamic effects of eribulin mesylate.

The anti-proliferative effects of eribulin mesylate were studied *in vitro* and were compared to the microtubule destabiliser vinblastine and the microtubule stabilizer paclitaxel in six cultured human cancer cell lines. The inhibitory effect of eribulin mesylate on different phases of cell cycle was also evaluated using flow cytometric analyses. In these studies eribulin mesylate inhibited growth of a wide range of established human cancer cell lines at IC50 values in the nanomolar range via a tubulin-based antimitotic mechanism, leading to G2/M block (Gap 2/mitosis stages of cell cycle). The *in vitro* potency of antiproliferative activity was: eribulin mesylate (average IC50 value of 1.11±0.27 nM), vinblastine (average IC 50 value of 1.21±0.1 nM), paclitaxel (average IC50 value of 4.60±0.25 nM). The IC 50 values were far below the clinically expected C_{max} value of 0.48 µM after 3 weekly doses of 1.23 mg/m^2 of eribulin.

A study evaluating the IC50 value for inhibition of the rate of tubulin polymerisation showed values for rate and extent of polymerisation after 60 minutes of 15.3 and 3.08 µmol/l (rate) and 39 µM and 4.67 µM (extent) for eribulin mesylate and vinblastine respectively.

The antiproliferative effects of eribulin mesylate were also studied on both non-permeability glycoprotein (P-gp)-expressing and P-gp-overexpressing human cancer cells where eribulin mesylate was shown to be a substrate for the P-gp drug efflux pump, and thus showed reduced *in vitro* potency against human cancer cells expressing high levels of P-gp.

The activity of eribulin mesylate against taxol resistant cancer cell was studied *in vitro* (study CAIVT 0107). Eribulin mesylate showed activity against 1A9PTX10 and 1A9PTX22 cancer cells which are both taxane (paclitaxel)-resistant based on distinct mutations in β-tubulin. Eribulin mesylate showed activity comparable to that of vinblastine with no significant resistance (resistance ratios approximately 1.3 in both cell lines).

Combinations of eribulin mesylate and docetaxel led to mostly additive inhibition of *in vitro* proliferation of the four breast cancer cell lines studied. Effects of combining eribulin mesylate with carboplatin in four non-small cell lung cancer cell lines varied from additive to moderately antagonistic depending on the cell line under study.

With regard to *in vivo* studies, eribulin mesylate in the 0.05-1.69 mg/kg dose range was shown to have anticancer activity against a variety of human cancer xenograft models grown subcutaneously in

athymic mice. Different dosing schedules for administration of eribulin mesylate as monotherapy in human breast cancer xenograft were tested and suggested that intermittent dosing such as Q2Dx3 [3 weeks] and Q4Dx3 are the most effective and least toxic schedules of administration compared to daily dosing regimens.

Treatment with eribulin mesylate was studied in combination with capecitabine, erlotinib, gemcitabine, doxorubicin or pemetrexed in human breast or human lung cancer xenograft models. Combination with capecitabine, erlotinib or gemcitabine showed enhancement of activity, whereas this was not the case with doxorubicin or pemetrexed (data not shown).

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies have been submitted.

Safety pharmacology programme

The safety pharmacology programme consisted of six *in vitro* and *in vivo* studies evaluating the effects of eribulin mesylate on the following organ systems: cardiovascular, respiratory, central nervous, and peripheral nervous systems.

Cardiovascular system

Two *in vitro* electrophysiological studies were conducted to assess the effects of eribulin mesylate on human ether a-go-go related gene (hERG) potassium currents in HEK 293 cells stably transfected with hERG and action potential parameters in the isolated dog Purkinje fibres. The *in vivo* effects of eribulin mesylate on the cardiovascular system were evaluated in beagle dogs.

In the HEK 293 cells, decreases in the tail current after 15 minutes of exposure were 16.4, 23.2 and 76.4% for vehicle, eribulin mesylate (30 µmol/L) , and positive control respectively. Thus, there was a minor indication of hERG inhibition with eribulin mesylate at a concentration which is approximately 60 times above the expected clinical C_{max} of 0.48 µM. Treatment with 1, 10 or 30 µmol/L of eribulin mesylate produced no effects on the cardiac action potentials in the isolated dog Purkinje fibre.

Intravenous infusion of eribulin mesylate at 0.04 mg/kg for 60 minutes to conscious beagle dogs, on days 1, 8 and 15 in male and 3, 10 and 17 in female dogs (Study SPT03-001) transiently decreased the systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and heart rate and increased the QT and RR intervals in both male and female dogs. However, when QT was corrected for changes in RR interval, there was no change in QTcF or QTcQ. The highest tested dose (0.04 mg/kg) resulted in an exposure that was lower than the clinical. Therefore the potential risk for cardiac arrhythmias has not been adequately evaluated in non clinical studies. However an additional study in dogs with high bolus dose to exceed the clinical exposure is not considered necessary given that a clinical study was conducted and a warning related to QT prolongation was added in section 4.4 of the SmPC.

Respiratory system

Eribulin mesylate was administered intravenously to Fischer 344 rats (6/group) via a tail vein at 0.1 or 0.25 mg/kg and the effects compared to morphine 20 mg/kg (study SPR03-003). Respirations rate and tidal volume were recorded at 30, 60, 120, 240, and 480 min post-dose.

Intravenous administration of the highest dose of eribulin mesylate (0.25 mg/kg) to rats caused a significant decrease ($p < 0.05$) in respiration rate at 120 min post dose when compared to the vehicle, but the decrease was not significant compared with the baseline value for the 0.25 mg/kg group. Rats treated with morphine exhibited all the known pharmacological effects.

Central nervous system

Eribulin mesylate was injected intravenously once to male Fischer 344 rats (6/group) via a tail vein at 0.1 or 0.25 mg/kg and the effects of this exposure on Irwin test parameters were compared to that of 2 mg/kg chlorpromazine. No consistent gross behavioural or physiological changes were recorded during the post-dose observation periods for any animal receiving either vehicle or eribulin mesylate. Rats treated with 2 mg/kg chlorpromazine exhibited all the known pharmacological effects.

Peripheral Nervous System

Neuropathy is a known adverse effect of inhibitors of tubulin polymerisation and microtubule dynamic such as paclitaxel. Study PPC-2009-01 investigated the neurotoxicity potential of eribulin mesylate, doses of 0.44, 0.88, 1.31 and 1.75 mg/kg were administered to BALB/c mice on a Q2Dx3 [x 2 weeks] schedule (Area under the plasma concentration time curve (AUC) at 1 mg/kg/day of 308 ng*hr/ml). The neurotoxic effects of eribulin mesylate on peripheral nerves were compared with that of paclitaxel 24 hours after the last treatment in the same study. Eribulin mesylate induced no significant reduction in nerve conduction velocity or peak nerve amplitude in caudal and digital nerves, which were significantly decreased upon treatment with paclitaxel. Some mild morphological changes consistent with axonopathy were evident in sciatic nerve and dorsal root ganglia of eribulin mesylate treated mice, but only at the 0.75 x maximum tolerated dose (MTD) (1.31 mg/kg dose) and higher.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions study has been submitted for eribulin mesylate. As part of the primary pharmacodynamic evaluation, combination studies with other anticancer agents *in vitro* and *in vivo* have been conducted (data not shown).

2.3.3. Pharmacokinetics

The pharmacokinetics of eribulin mesylate was evaluated by *in vivo* studies in mice, rats and dogs. For assessments of absorption, metabolic characteristics and drug-drug interaction, *in vitro* studies with Caco-2 cells, hepatocytes, liver microsomes or other sub-cellular fractions of the liver were also conducted. Although none of the studies were GLP compliant they were performed at facilities used for operating in accordance with the principles of GLP.

An LC-MS/MS method was developed and validated for the quantisation of eribulin mesylate in mouse, rat, dog and human plasma. The detection ranges varied from 5-200 ng/ml (mouse) to 2-200 ng/ml (dog). Improvement of the method extended the range to 0.1-1000 ng/ml. ^{14}C-Eribulin acetate was used in radiotracer studies in rats and dogs. The concentration of radioactivity in the blood, urine and faeces was determined by liquid scintillation spectrometry.

Absorption

The pharmacokinetics of eribulin mesylate has been examined after single or repeated IV or *Per os* (PO) administration *in vivo* in mice (four different strains), rats (2 strains) and dogs.

Eribulin mesylate had low bioavailability after PO administration in mice and rats (< 7% and < 3%, respectively). Pharmacokinetic data obtained in permeability-glycoprotein (P-gp) deficient mice and in rats co-administered orally with cyclosporine (a P-gp inhibitor) suggested that the drug efflux pump P-gp was a major factor contributing to the low oral bioavailability of eribulin mesylate. The peak plasma concentration following PO administration was generally observed within 4 hours post-dosing in mice and rats.

When eribulin mesylate was administered intravenously, its pharmacokinetic behaviour was fairly consistent in the investigated species except in the mouse. Salient findings after single or repeated intravenous administrations were large distribution volume, slow to moderate clearance, and fairly long terminal half life (4-10 h in mice, 4-28 h in rats, and 11-45 h in dogs versus 24-66 h in human). Despite slow clearance, there was no obvious accumulation of eribulin mesylate with the infusion schemes used for repeated dosing.

Plasma protein binding differed somewhat but was only moderate in all investigated species (<36%), including human (49-65%).

Distribution

The tissue distribution of radioactivity derived from drug following a single IV administration of ^{14}C-eribulin acetate was evaluated in male non-pigmented and pigmented rats by quantitative whole-body autoradiography. The distribution results showed that eribulin mesylate is widely distributed to most organs and tissues (lung, urinary bladder, renal cortex, renal medulla, liver, spleen, thyroid, stomach and salivary gland), except the central nervous system (CNS). High concentrations were found in bile, which is likely to be a major route for excretion. Comparison of data from pigmented and non-pigmented animals did not suggest any affinity to melanin. Only male animals were included in the study. The potential of eribulin mesylate to pass the placenta and its ability to transfer into breast milk have not been investigated. However, embryo-foetal developmental toxicity in rats suggests that eribulin mesylate and/or its metabolites pass through the placenta and are distributed to the foetus.

In mice, eribulin mesylate showed penetration into LOX human melanoma tumour xenografts following single or multiple IV administrations with tumour exposures approximately 20 to 30 times higher than that in plasma. The plasma concentration profile in LOX-mice was not different from that of tumour free mice.

With regards to the blood distribution, the applicant has provided additional data indicating that association of eribulin mesylate to blood cells is negligible and thus that plasma is a suitable matrix for monitoring eribulin mesylate exposure levels in dogs, rats and humans.

Metabolism

From *in vitro* and *in vivo* metabolic studies, twelve putative metabolites of eribulin mesylate were identified or postulated. *In vitro* studies in human liver microsomes suggested that CYP3A4 is the main enzyme involved. Two studies in rats and dogs, respectively, were also conducted. ^{14}C-eribulin acetate was administered intravenously and samples of plasma, urine, faeces, and bile (rat only) were analysed with LC-MS-radio-flow detection. Unchanged eribulin was the major component found in both species. Overall, the metabolism of eribulin mesylate *in vivo* was limited and unchanged parent substance dominated. There were some species differences with a higher degree of metabolism in the rat than in the dog but these differences were not considered to have a major impact on the interpretation of the animal toxicity studies.

Elimination

The excretion patterns after a single IV dose in rat and dog showed that eribulin mesylate is eliminated mainly via faeces. Faecal excretion was relatively rapid, occurring largely within the first 72 hours in all species. Urinary excretion accounted for 8-16% of the administered dose across all species.

Interactions

Drug-drug interactions were evaluated *in vitro* with Caco-2 cells, hepatocytes, liver microsomes or other sub-cellular fractions of the liver. Eribulin mesylate was shown to be a substrate for the

transporter P-gp *in vitro*. However, considering that the IC50 value was >10 µM, P-gp inhibition from eribulin mesylate was not considered clinically relevant following administration of therapeutic dosages (>26-fold safety margin). Eribulin mesylate was shown to inhibit CYP3A4-mediated nifedipine dehydration, warfarin and testosterone hydroxylation. *In vitro* inhibition on eribulin mesylate metabolism of co-administered drugs was also investigated. In contrast to the potent inhibition shown by ketoconazole in the suspensions of human primary hepatocytes, eribulin mesylate elicited weak inhibitory effects on the CYP3A4-mediated metabolic pathways of carbamazepine, diazepam, paclitaxel, midazolam, tamoxifen and terfenadine in a concentration-dependent manner.

2.3.4. Toxicology

Single dose toxicity

No single-dose toxicology study has been submitted.

Repeat dose toxicity

The toxicological programme consisted of six repeat dose toxicity studies (subchronic and chronic) conducted as IV infusion studies in rats and dogs. All except one supportive study (study G465520A) were conducted according to GLP principles.

In these studies, eribulin mesylate was dissolved in 5% ethanol in saline, and was administered intravenously. The infusion time was approximately 1 minute in rat and 1 hour in dogs. The planned infusion time in man is 2-5 minutes. The applied treatment schedule in the subchronic studies was 3 doses administrated with 4 or 7 days interval (Q4D×3 or Q7D×3) followed by 3, 14 or 26 days recovery period; the chronic studies applied 6 treatment cycles with 3 times weekly treatments followed by 14 days recovery period.

Animals were sacrificed at days 12 and 35 for the Q4Dx3 schedule and days 18 and 29 in the Q7Dx3 schedule. The following parameters were assessed: dose analysis, mortality and clinical observations, body weight, clinical pathology (haematology and clinical chemistry), gross pathology and histopathology (Table 1).

Table 1. Summary of the repeat-dose studies.

Study ID **Duration**	**Species/ Number/ Sex/ Group**	**Dose of eribulin mesylate (mg/kg)/ Route**	**MTD/NOAL (mg/kg)**
G465520A (Non-GLP) 15 days DRF study	F344 rats / 3-4 Males	0, 0.1, 0.25, 0.5, 0.75, 1.0, 1.5 , 2.0 ER-86526 (NSC-707389) / IV (1 minute infusion) Day 1, 5 and 9.	MTD <0.25 (1.5mg/m2) Q4Dx3
G465520C (GLP) 12 days study with 26 days recovery period	F344 rats/ 5 Males +5 Females / main group 5 Males+5 Females / recovery group	0, 0.013, 0.13, 0.2 ER-86526 (NSC-707389-K/D6) / IV (1 minute infusion) Day 1, 5 and 9	NOAEL 0.013 MTD 0.2mg/kg
7306 (GLP) 18 days study with 14 days recovery period	F344 rats/ 5 Males+5 Females / main group 5 Male +5 Female / recovery group	0, 0.1, 0.2, 0.25 ER-86526 (BLDR001)/ IV (1 minute infusion) Day 1, 8 and 15	NOAEL not determined MTD 0.1mg/kg
7640 (GLP) 169 days (~6 months) study with 14 days recovery period following each cycle	F344 rats/ 15 Males +15 Females No main sacrifice i.e. all animals killed 14 days after last treatment	0, 0.015, 0.05, 0.15 ER-86526 (BLDR001)/ IV (1 minute infusion) Day 1, 8 and 15 x 6 Last treatment day 155	NOAEL not received due to changes in the liver, testis and bone marrow
G465520B (GLP) 22 days MTD study	Beagle dogs/ 1 Male +1 Female / group	0, 0.03, 0.075 NSC-707389 (570-285D) / IV (1 hour infusion) Day 1, 5 and 9	MTD >0.03mg/kg
G465520D (GLP) 12 days study with 26 days recovery period	Beagle dogs/ 1 Male +1 Female / main group/ 1 Male +1 Female / recovery group	0, 0.004, 0.03, 0.04 NSC-707389-K/D6 (OH0499) / IV (1 hour infusion) Day 1, 5 and 9	NOAEL 0.004mg/kg
6288 (GLP) 18 days study with 14 days recovery period	Beagle dogs / 3 Males+3 Females No main sacrifice i.e. all animals killed 14 days after last treatment	0, 0.02, 0.04, 0.05 ER-086526 (BLDR001)/ IV (1 hour infusion) Day 1, 8 and 15 Actual dose approx. 30% lower due to incorrect handling of formulation (adhesion to plastic vials/filters)	NOAEL <0.02mg/kg MTD >0.05mg/kg
6528 (GLP) 169 days (~6 months) study with 14 days recovery period following each cycle	Beagle dogs/ 4 Males + 4 Females No main sacrifice i.e. all animals killed 14 days after last treatment	0, 0.0045, 0.015, 0.045 ER-086526 (BLDR001)/ IV (1 hour infusion) Day 1, 8 and 15 X6 Last treatment day day 155	NOAEL 0.015mg/kg

In the repeat dose range finding studies, a single dose of 0.75 mg/kg/day or higher caused severe toxicity leading to sacrifice 3-4 days after dosing in rats. Two doses of 0.075 mg/kg/day (given day 1 and 5) were lethal to dogs (diarrhoea, emesis correlated with intestinal histopathological changes). No mortality in immediate association with dose administration was observed in any study.

In all the repeat-dose toxicity studies in both rats and dogs, eribulin mesylate produced bone marrow toxicity represented by a decrease in the counts of peripheral blood cells, including red blood cell

(RBC), white blood count (WBC), neutrophil (SEG), reticulocyte (RET) and/or RBC-related parameters, and depletion of bone marrow cells on histopathological evaluation. Comparison of IC50 values for proliferation of Colony forming cell-granulocyte, erythrocyte, macrophage, megakaryocyte (CFC-GEMM) bone marrow progenitor cells for eribulin mesylate, vinblastine and paclitaxel showed that dogs were somewhat more sensitive than humans for the inhibitory effect of these drugs on the expansion of these bone marrow cells. Lymphoid and testicular toxicity were other eribulin mesylate-related side effects in both rats and dogs. These toxicities appeared at 0.10 mg/kg, single cycle Q7Dx3 (study 7306) and 0.03 mg/kg, single cycle Q4Dx3 in rats and dogs, respectively (studies G465520B and G465520D). Histopathological changes of the skeletal muscle (degeneration) and sciatic nerve (neurofiber degeneration) were also noted in rats alone at ≥0.20 mg/kg (≥1.20 mg/m^2). All the signs of toxicity, except for the changes in the testes and rat sciatic nerve, were reversible, sometimes with a compensatory rebound response of the hematopoietic system.

Clinical signs of intestinal toxicity such as emesis and diarrhoea correlated to regenerative hyperplasia in the crypts/glands of the small and large intestine and small intestine villous atrophy were shown in dogs receiving two doses of 0.075 mg/kg/day eribulin mesylate in a Q4Dx3 scheme.

In the chronic rat study (study 7640), 9 animals died (one control, 4 females on 0.015 mg/kg, 2 females at 0.05 mg/kg and 2 females at 0.15 mg/kg) after ≥120 days from the start of the treatment. In these animals, undigested food was found in the oral cavity or larynx. The presence of stomach ingest in the upper respiratory system was associated with changes in the lungs such as varying degrees of inflammation and alveolar edema and histocytosis.

Another organ that showed signs of toxicity upon treatment with eribulin mesylate in repeated dose toxicity studies was the liver. Liver necrosis (doses of ≥0.015mg/kg) was observed in the chronic rat study (study no. 7640), with increase in relative and absolute liver weights shown in the highest dose group (≥0.15mg/kg). Changes in the liver mostly corresponded to simultaneous increase in aspartate aminotransferase (AST)/alanine aminotransferase (ALT) but liver necrosis at doses of ≤0.15mg/kg did not appear to correlate with an increase in these values. The applicant provided further analysis of the observed changes and considered the lesions not to be directly related to the test article but more likely to be the result of bacterial infections related to severe bone marrow toxicity.

Decrease in the level of electrolytes (Na^+, K^+ and CL^-) together with increased blood urea nitrogen (BUN) was observed in dogs treated with a single cycle Q4D×3 of eribulin mesylate (study G465520B). In rats (study G465520A) fluctuations in sodium, glucose and creatinine have also been observed. Additionally, rats receiving doses of ≥0.05 mg/kg in 6 months (study 7640) showed increased absolute and relative kidney weight which were not correlated to any histopathological or electrolyte changes.

Genotoxicity

Genotoxicity was evaluated in both *in vitro* and *in vivo* studies. The studies consisted in three bacterial mutations assays (Ames test), two *in vitro* genotoxicity studies in mammalian cells (mouse lymphoma mutation assays) and one *in vivo* micronucleus assay in Rats.

Eribulin mesylate was not mutagenic in the Ames test, either with or without rat liver S9 metabolising system, but was positive in the L5178Y/TK+/- mouse lymphoma mutagenesis assay. No increase in *in vitro* genotoxicity was observed in the presence of higher amounts of impurities. In the *in vivo* rat micronucleus assay, eribulin mesylate was clastogenic, inducing substantially larger micronuclei than those induced by cyclophosphamide. The generally large sized micronuclei induced by eribulin mesylate indicated that the effect was due primarily to chromosome segregation interference rather than to chromosome breakage, which are expected findings for anti-tubulin agents.

Carcinogenicity

No carcinogenicity study has been submitted.

Reproduction Toxicity

Neither fertility study nor pre-post natal development study has been submitted with eribulin mesylate.

In the embryo-foetal developmental toxicity study in rats (Study LFA00033), eribulin mesylate was administered as a slow bolus injection to female rats (8 animals/dose) once a day on Gestation Days (GD) 8, 10 and 12 at doses of 0, 0.01, 0.03, 0.10 or 0.15 mg/kg.

Decreased body weight (up to -30.3%) and food consumption (up to -27.3%) were observed during and post dosing period at 0.10 and 0.15 mg/kg. One female at 0.15 mg/kg delivered prematurely, and was sacrificed on GD 21. Eribulin mesylate-related clinical signs in dams included pale extremities, scant faces and dehydration at 0.15 mg/kg. There were also an increase in the number of early resorptions at 0.10 and 0.15 mg/kg. Three litters were completely resorbed at 0.15 mg/kg. Decrease of foetal body weight was also noted at 0.10 and 0.15 mg/kg doses. External and/or soft tissue anomalies (absence of lower jaw, tongue, stomach and spleen) were noted at 0.15 mg/kg, indicating that eribulin mesylate possesses teratogenic potential. The no observed adverse effect level (NOAEL) was 0.03 mg/kg for maternal general toxicity, reproductive function, and embryo-foetal development.

Toxicokinetic data

Pharmacokinetic data were collected as part as the repeat dose toxicity studies. The exposure to eribulin mesylate after repeated dosing appeared to increase with the dose in both rats and dogs. Significant accumulation of eribulin mesylate was not observed after either Q4D×3 or Q7D×3 dosing schedule. Values of AUC showed some fluctuations among animals sometimes with no apparent dose-dependent differences (study G465520D in dogs, Table 2).

Table 2. Inter species comparison pharmacokinetics data on Eribulin mesylate in rats, dogs and humans.

Study ID	Daily Dose/Interval/species (mg/kg)	AUC (ng.h/ml)		Cmax ng/ml	
		♂	♀	♂	♀
6528	0.045 Weekly dogs	27.391-30.663	16.339-24.078	18.300	15.766
6288	0.04 Weekly dogs	22.978	14.495	-	-
7640	0.05 Weekly rats	16.868-19.230	18.635-27.736	35.096	37.170
G465520B	0.075 Bi-weekly dogs	1959.4	3071.7	108	131
G465520D	0.04 Bi-weekly dogs	102.7-115.55	85.35-106.63	37.4-52.3	28.0-36.3
Human	weekly		913		247

Local Tolerance

Although no local tolerance study has been conducted, local effects to injection and infusion sites of eribulin mesylate solution were evaluated macro- and microscopically in the repeated dose toxicity studies in rats (Studies 7306 and 7640) and dogs (Studies G465520B, G465520D, 6288 and 6528). In those studies, no eribulin mesylate-related effects at injection and infusion sites were observed.

No non clinical data following paravenous administration were submitted.

Other toxicity studies

In vitro Myelotoxicity studies

Eribulin mesylate was tested for toxicity to cultured bone marrow cells from mouse, human and dog (DSD2001-06, DSD2001-07, and DSD2001-08). A similar comparative study was conducted with three different compounds including Eribulin mesylate active substance and the marketed drugs Paclitaxel and Vinblastine. IC50 values for inhibition of colony formation of Colony forming unit-granulocyte, macrophage (CFU-GM) cells using colony forming assays (Hipple´s soft agar assay) and inhibition of proliferation of CFC-GEMM cells using Hematotoxicity Assay via Luminescence Output (HALO) were calculated. The sensitivity of dog and human bone marrow to the toxicity of eribulin mesylate was similar to IC50 around 15 nM.

Impurities studies

Four degradation products (ER-814363, ER-814365, ER-814366, and ER-809307) have been observed at levels above the ICH Q3B (R2) reporting threshold (i.e. >0.1%) in primary stability studies for eribulin mesylate injection. The batches applied for the toxicological studies contained impurities in concentration above the proposed acceptance criteria (limits) for drug product except the degradation product ER-809307 which has been observed at 0.65% in study S09043.

A repeat dose toxicity study on impurities of eribulin mesylate was conducted in F344 rats (Study S09043). Eribulin mesylate from high impurity batch (including residual solvents and metals) was administered as a slow bolus injection to female and male rats (10 animals/group/sex) once a day on 1, 8 and 15 at doses of 0, 0.1 or 0.2 mg/kg. On completion of treatment, animals (5/group/sex) were subjected to necropsy 3 days (on Day 18) and 14 days (on Day 29) after the last administration. The study showed no additional toxicity which could be related to these impurities (data not shown).

2.3.5. Ecotoxicity/environmental risk assessment

The Applicant has submitted an environmental risk assessment. The calculated PEC-value was below the action limit of 0.01 µg/L and a Phase II environmental fate and effect analysis was not deemed necessary. Nevertheless, the Applicant conducted a limited programme to establish an environmental toxicity and fate profile. These data did not raise any additional concerns, considering the low estimated exposure. Eribulin mesylate is also not considered a persistent, bioaccumulative and toxic substance as log Kow did not exceed 4.5.

2.3.6. Discussion on non-clinical aspects

Halaven (eribulin mesylate) is a non-taxane, microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. It is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*. Eribulin

mesylate inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. Eribulin mesylate exerts its effects via a tubulin-based antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

In primary pharmacodynamic studies, eribulin mesylate inhibited growth of a wide range of established human cancer cell lines at IC50 values in nanomolar range. It turned out to be a substrate for the P-gp drug efflux pump, and thus shows reduced *in vitro* potency against human cancer cells expressing high levels of P-gp. Eribulin mesylate showed activity against 1A9PTX10 and 1A9PTX22 cancer cells that have β-tubulin mutations and therefore are taxane (paclitaxel)-resistant. Combinations of eribulin mesylate and docetaxel led to mostly additive inhibition of *in vitro* proliferation of the four breast cancer cell lines studied, whereas combination with carboplatin varied from additive to moderately antagonistic depending on the cell line. Finally, in-vivo studies have shown that eribulin mesylate generally has anticancer activity against a variety of human cancer xenograft models grown sc in athymic mice. However, these models have low fidelity to the actual environment in which the tumour cells proliferate, they lack the relevant tumour-stroma interactions which are necessary for tumour development, progression and metastatic spread and they are generally of limited value to predict the effect in patients with metastatic breast cancer or advanced ovarian cancer.

No secondary pharmacodynamics studies have been submitted for Halaven due to the non-specific cytotoxicity of eribulin mesylate as a microtubule growth inhibitor and the significant toxicity of microtubule inhibitors. The lack of secondary pharmacodynamics studies is considered acceptable.

The exposure achieved in the in-vivo safety pharmacology studies is generally much lower than the expected human exposure. Toxicity studies conducted in dogs suggested that dosing of eribulin mesylate resulting in higher exposure may be feasible to administer (study G465520B: C_{max} of ~100 ng/ml with a dose of 0.075 mg/kg iv; Study DSD2002-42: AUC of ~100ng*h/ml with a dose of 0.08 mg/kg iv, via cephalic vein).

Study PPC-2009-01 clearly showed that eribulin mesylate, as expected, affects peripheral nerve function. Also results from the repeat dose toxicity studies gave further support to this conclusion. Whether there is difference compared to the effects of paclitaxel cannot be decided based on this study.

Salient features of the pharmacokinetic profile of eribulin mesylate after single or repeated intravenous administrations included large distribution volume, slow to moderate clearance and fairly long terminal half life. Despite slow clearance, there was no obvious accumulation of eribulin mesylate with the infusion schemes used for repeated dosing. Exposure after repeated dosing appeared to increase with dose in both rats and dogs. Plasma protein binding differed somewhat but was only moderate in all investigated species. The distribution results showed that eribulin mesylate is widely distributed to most organs and tissues, except the CNS. High concentrations were found in bile, which is likely to be a major route for excretion. Eribulin mesylate is eliminated mainly via the faeces.

Twelve putative metabolites of eribulin mesylate were identified or postulated and *in vitro* studies in human liver microsomes suggest that CYP3A4 is the main enzyme involved. However, the metabolism of eribulin mesylate in vivo was limited and unchanged parent substance dominated. There were some species differences with a higher degree of metabolism in the rat than in the dog but these differences are not believed to have a major impact on the interpretation of the animal toxicity studies.

For discussion on pharmacokinetic interactions please refer to Clinical Pharmacology.

As expected, in the repeat-dose toxicity studies, eribulin mesylate caused bone marrow toxicity and lymphoid and testicular toxicity at the lowest doses tested in the rat and dog. Histopathological changes of the skeletal muscle (degeneration) and sciatic nerve (neurofiber degeneration) were also noted in rats alone. All the signs of toxicity, except for the changes in the testes and rat sciatic nerve, were reversible. In addition toxicity results at the high dose have identified the liver as a target organ for toxicity. Possible signs of toxicity were also found on renal markers. However, it is likely that the altered changes are attributable to loss of protein and electrolytes from the gastrointestinal tract and pre-renal BUN increase from dehydration and poor renal perfusion as suggested by the applicant. Signs of intestinal toxicity such as emesis and diarrhoea were shown in dogs. The presence of stomach ingest in the upper respiratory system was associated with changes in the lungs such as varying degrees of inflammation and alveolar edema and histocytosis. The applicant referred to these effects as spontaneous oesophagectasis which is reported specifically in the F344 rat in two publications dated to 1979 and 1986. Although it is not possible to determine the exact cause of these the syndrome described above may be one possible cause. These findings are however considered being of questionable clinical relevance.

This pattern of toxicity matches the bio-distribution pattern of eribulin mesylate in the albino rats shown in the pharmacokinetic studies and also the most common adverse effects reported in the clinic.

No single-dose toxicology study has been submitted which is in accordance with the current recommendations from the European guidelines (CHMP/SWP/302413/08 and EMA/CHMP/SWP/81714/2010).

No carcinogenicity study has been submitted which is acceptable since according to the guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals S9, ICH Tripartite Guideline 29th October 2009, carcinogenicity studies are not warranted for products intended to treat patients with advanced cancers.

Fertility studies were not submitted with eribulin mesylate. Adequate justifications have been provided based on repeated-dose studies where irreversible testicular toxicity has been observed in both rats (hypocellularity of seminiferous epithelium with hypospermia/aspermia and dogs. Thus, male fertility may be compromised by treatment with eribulin mesylate based on its mechanism of action. Additionally, due to a trend toward dose dependent reduction in the numbers of implantation sites shown when pregnant rats were exposed to eribulin mesylate, an effect of eribulin mesylate on female fertility cannot be excluded. Eribulin mesylate is embryotoxic, phototoxic, and teratogenic in rats. No pre-post natal development study has been performed which is acceptable for this type of product. Overall, the toxicity profile is as expected for this class of compounds.

No non clinical data following paravenous administration were submitted. However, the applicant has provided and discussed data on extravasation in clinical trials where one case out of 1318 patients was experienced.

The non-clinical safety assessment program, although extensive and conducted in relevant species, had some inherent limitations regarding the toxicity profiles obtained through the applied design of the subchronic and chronic toxicity studies in rat and dog. Especially the pathology routines in these studies were not conducted according to current standards of relevant guidelines. Therefore it cannot be excluded that some low grade or low incidence toxicities, plus delayed toxicities and pathology changes with short reversibility remain unidentified. However, in the current situation clinical data has provided substantial information regarding human toxicities.

2.3.7. Conclusion on the non-clinical aspects

In conclusion, eribulin mesylate inhibits tumour cell growth *in vitro* in a wide range of established human cancer cell lines. Administration of eribulin mesylate in intermittent dosing schedule showed anticancer effects against a variety of human xenograft models.

Overall, the pharmacokinetics of eribulin mesylate was characterised by an extensive volume of distribution and a slow to moderate rate of clearance.

The safety pharmacology studies suggest that eribulin mesylate has a low potential for exerting adverse effects on the respiratory and central nervous systems. *In vitro* studies did not show any adverse effects of eribulin mesylate on the hERG potassium currents and action potential parameters. However, the potential risk of eribulin mesylate for cardiac arrhythmias has not been adequately evaluated in non clinical studies. However further *in vivo* investigation is not considered necessary given that a clinical study was conducted and a warning related to QT prolongation was added in section 4.4 of the SmPC.

Overall, the toxicity profile of eribulin mesylate is consistent with the expected effects of a microtubule disruptor.

With regards to genotoxicity, eribulin mesylate was positive in the mouse lymphoma mutagenesis assay and was clastogenic in the *in vivo* rat micronucleus assay.

The toxicology programme revealed toxicity effects of eribulin mesylate on embryo-foetal development (including teratogenicity) and fertility. Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Halaven. Furthermore, women are advised to avoid pregnancy while they or their partner are on eribulin mesylate therapy and up to 3 months after treatment due to the embryotoxic, teratogenic potential of eribulin mesylate. There is no information on the excretion of eribulin mesylate or its metabolites in animal breast milk which has been reflected in section 4.6 of the SmPC. Breastfeeding is contraindicated in patients treated with eribulin mesylate.

2.4. Clinical aspects

2.4.1. Introduction

12 clinical Studies were submitted in support of the clinical efficacy and safety of eribulin. These studies are listed in Table 3 below. Moreover, 8 *in vivo* studies and 8 *in vitro* studies using human biomaterials comprised the clinical pharmacology programme (studies not shown).

The indication applied for initially was the following:

- HALAVEN monotherapy is indicated for the treatment of patients with breast cancer who have received at least two chemotherapeutic regimens for locally advanced or metastatic disease (see section 5.1).

The finally approved indication is as follows:

- HALAVEN monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease (see section 5.1). Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

The recommended dose of eribulin as the ready to use solution is 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 eribulin mesylate) which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle. For further dosing recommendation, please refer to section 4.2 of the SmPC.

GCP

The Clinical trials were performed in accordance with good clinical practice (GCP) as claimed by the applicant

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

- Tabular overview of clinical studies

Table 3. Clinical Efficacy and Safety studies

Study ID	Design; Control Type	Subjects by Arm; Enrolled/ Treated	Endpoints	Study and Control Drugs Dose, Route, Regimen
E7389-A001-101 "Study 101"	Phase 1, Open-label, non-randomised, dose-finding study in subjects with advanced solid tumours	33/32	MTD, PK, tumour response and safety	Eribulin mesylate IV (1-hour infusion); 0.25, 0.5, 0.7, 1 or 1.4 mg/m^2
E7389-A001-102 "Study 102"	Phase 1, Open-label, non-randomised, multi-center, dose-finding study in subjects with advanced solid tumours	21/21	MTD, PK, tumour response and safety	Eribulin mesylate IV (1-hour infusion) 0.25, 0.5, 1, 2, 2.8 or 4 mg/m^2
E7389-E044-103 "Study 103"	Phase 1, Open-label, non-randomised, radiotracer, metabolism, mass-balance and treatment study in subjects with advanced solid tumours	6/6	PK, excretion, mass balance, metabolic pathway, safety and efficacy	C1 Day 1: One IV dose of ^{14}C-eribulin (2mg, approx 80 to 90 µCi) C1 Day 8: unlabeled eribulin mesylate(1.4 mg/m^2 IV over 2-5 min). Extension Phase: unlabeled eribulin mesylate(1.4 mg/m^2 IV)
E7389-J081-105 "Study 105" [a]	Phase 1, Open-label, dose-ascending study in subjects with advanced solid tumours	15/15	MTD/DLT, preliminary efficacy, safety and tolerability, PK	Eribulin mesylate 0.7, 1, 1.4 or 2 mg/m^2 (2-10 min IV bolus)
E7389-E044-108 "Study 108"	Phase 1, Open-label, three-parallel group PK study in subjects with advanced solid tumours with normal or impaired hepatic function	6 normal 7 mild hepatic impairment 4 moderate hepatic impairment 17/17	PK, efficacy and safety	Eribulin mesylate 5 min bolus IV infusion 1.4 mg/m^2 (normal hepatic function) 1.1 mg/m^2 (mild hepatic impairment) 0.7 mg/m^2 (moderate hepatic impairment 0.7, 1.1, 1.4 mg/m^2)
E7389-E044-109 "Study 109"	Phase 1, Randomised, open-label, two-way crossover, two sequences of eribulin and ketoconazole administration and coadministration in subjects with advanced solid tumours	6 12/12	Influence of ketoconazole (potent CYP3A4 inhibitor), on PK, safety and tolerability	Cycle 1: Group 1 eribulin mesylate Day 1 (1.4 mg/m^2), combo eribulin mesylate (0.7 mg/m^2) & ketoconazole (200 mg) Day 15, ketoconazole Group 2: combo eribulin mesylate (0.7 mg/m^2) & ketoconazole (200 mg) on Day 1, ketoconazole (200 mg) Day 2, eribulin mesylate (1.4 mg/m^2) Day 15.
E7389-E044-110 "Study	Phase 1, open-label, multi-center, single-arm, study in subjects with	31/26	Impact on ECG, as measured by QT/QTc interval and PK/PD	Eribulin mesylate 1.4 mg/m^2 2-5 min IV bolus

110"	advanced solid tumours		analysis. PK profile, safety and tolerability and best ORR using RECIST	
E7389-A001-201 "Study 201"	Phase 2, Open label, Simon 2-stage design, single-arm in subjects with MBC following an anthracycline and a taxane	104/103	Efficacy (ORR, DOR, PFS, OS), Safety	Eribulin mesylate 1.4 mg/m^2 IV bolus (5 min)
E7389-A001-202 "Study 202"	Phase 2, pen-label, single arm, stratified by prior taxane in subjects with advanced NSCLC	106 106/103	Efficacy (ORR, DOR, PFS, OS), safety and tolerability	Eribulin mesylate 1.4 mg/m^2 IV bolus (5 min)
E7389-G000-204 "Study 204"	Phase 2, multi-center, open-label, single-arm 2-stage design, stratified by prior taxane treatment in subjects with hormone refractory prostate cancer	No Prior Taxane Therapy: 58. Prior Taxane Therapy: 50 112/108	PSA response rate, duration of PSA response, PFS, ORR, DOR and safety	Eribulin mesylate 1.4 mg/m^2 IV bolus (2-5 min)
E7389-G000-211 "Study 211"	Phase 2, open-label, single arm study in subjects with locally advanced or MBC following anthracycline, taxane, and capecitabine	299/291	Efficacy (ORR, DOR, PFS, OS) , safety and PK/PD	Eribulin mesylate 1.4 mg/m^2 IV bolus (2-5 min)
E7389-G000-305 "Study 305"	Phase 3, open- label, randomised, parallel 2-arm, multi-center study vs. TPC in subjects with LR or MBC, previously treated with ≥2 and ≤5 prior chemotherapy regimens, including anthracycline and taxane	Eribulin: 508 TPC: 254 762/750	OS, PFS, ORR, DOR, Safety	Eribulin (1.4 mg/m²) IV bolus (2-5 min) TPC: single agent chemo-therapy, hormonal/ biological therapy, or best supportive care.

Duration of all studies was until ≥1 protocol-defined criteria occurred (related to safety, PD or unacceptable toxicity) or subject withdrawal for all studies above.

Grey shaded rows: Patients on target dose in these studies are pooled together as "Breast Cancer Population" (BCP).

[a] Study 105 was not included in pooled population as data were not available at the time of analysis.

Abbreviations: CRF: Clinical report form; F: female; M: male; B/W/O = Black/White/Other; TCP: treatment of the physician's choice; AE = Adverse event; CSR = clinical study report; DLT = Dose-limiting toxicity; DOR = Duration of response, ECG = electrocardiogram; IV = Intravenous; MTD = Maximum-tolerated dose; NDA = New Drug Application; NSCLC = Non-small cell lung cancer; ORR = Objective response rate (complete + partial response; Response Evaluation Criteria in Solid Tumors [RECIST] criteria); OS = Overall survival; PD = Pharmacodynamics; PFS = Progression-free survival; PK = Pharmacokinetics; PSA = Prostate-specific antigen; QoL = Quality of life.

2.4.2. Pharmacokinetics

Absorption

Eribulin is administered intravenously twice every 21-day cycle (once on Days 1 and once on Days 8).

Distribution

The pharmacokinetics of eribulin are characterized by a rapid distribution phase followed by a prolonged elimination phase, with a mean terminal half-life of approximately 40 h. It has a large volume of distribution (range of means 43 to 114 l/m^2).

Eribulin has a low protein binding (65, 49 and 50% binding at 100, 500 and 1000 ng/ml). The volume of distribution is relatively large with range of means from 43 to 114 L/m^2.

Metabolism

Eribulin mesylate has 19 chiral centres and is administered as one specific enantiomer. The degree of interconversion in man appears small. Although *in vitro* data suggested eribulin metabolism via CYP3A4, an *in vivo* mass-balance study (see elimination below) showed that drug elimination mainly takes place through biliary excretion of unchanged drug. Metabolite concentrations represented <0.6% of parent compound, confirming that there are no major human metabolites of eribulin.

Elimination

Clearance is low with average estimates varying from 1.16 to 2.42 l/h/m^2 following a dose of 1.23 mg/m^2. The terminal half-life is long (approximately 40 hours). No significant accumulation of eribulin was observed on weekly administration.

Based on a mass-balance study submitted (data not shown), no or very little metabolism of eribulin takes place and no metabolites have been identified in plasma *in vivo.* Eribulin is mainly eliminated through biliary excretion of unchanged drug. This route contributes to 70% of total clearance. The transporter involved has not been identified. If the secretion is completely inhibited, it could in theory give rise to a more than 3-fold increase in plasma concentrations.

After administration of ^{14}C-eribulin to patients, approximately 82% of the dose was eliminated in faeces and 9% in urine indicating that renal clearance is not a significant route of eribulin elimination.

Dose proportionality and time dependencies

The pharmacokinetic properties are not dose or time dependent in the range of eribulin mesylate doses of 0.25 to 4.0 mg/m^2, but results from one study indicated a decreased clearance with increasing dose (data not shown).

Special populations

Intra- and inter-individual variability

The variability in systemic exposure is relatively large. The coefficient of variation (CV) in AUC was on average about 45%. In the population analysis the inter-individual variability in clearance not explained by covariates was 46% CV. The inter-occasion (~intra-individual) variability was markedly lower being 14 %CV.

Renal impairment

A study in patients with different degrees of impaired renal function showed that the exposure of eribulin in patients with moderate renal function (creatinine clearance≥40 to 59 mL/min, n=6) was similar to in patients with normal renal function while the exposure in patients with severe impairment was increased by 75% (creatinine clearance<40 ml/min, n=4).

Hepatic impairment

A study evaluated the PK of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=4) hepatic impairment due to liver metastases. Compared to patients with normal hepatic function (n=6), eribulin exposure increased 1.8-fold and 2.53-fold in patients with mild and moderate hepatic impairment, respectively. Administration of eribulin at a dose of 0.97 mg/m^2 to patients with mild hepatic impairment and 0.62 mg/m^2 to patients with moderate hepatic impairment resulted in a somewhat higher exposure to eribulin than a dose of 1.23 mg/m^2 to patients with normal hepatic

function. Eribulin was not studied in patients with severe hepatic impairment (Child-Pugh C). No study in patients with hepatic impairment due to cirrhosis has been submitted.

Age

There were no indications from the population analysis that age has an impact on the systemic exposure and the analysis included 63 subjects ≥ 65 years. However, from a pharmacokinetic perspective there are limited data available for elderly above 80 years of age.

Weight

The variability in systemic exposure is to a large extent explained by differences in body weight, moreover the results from the population PK analysis support the Body surface area (BSA)-based dosing regimen.

Pharmacokinetic interaction studies

Information on pharmacokinetic interactions comes primarily from *in vitro* studies (see Non-Clinical aspects).

In clinical study E7389-E044-109, the DDI between ketoconazole and eribulin was investigated. Eribulin 1.23 mg/m^2 was injected during 2-5 minutes on day 1 followed by a washout and on day 15 eribulin 0.62 mg/m^2 was administered together with a ketoconazole 200 mg dose, which was administered also the following day. Blood sampling was performed for 144 hours after the eribulin doses. No effect of ketoconazole was observed (data not shown). Furthermore, the population pharmacokinetic model showed that concomitant administration of CYP3A4 inhibitors or CYP3A4 inducers did not alter the clearance of eribulin. A drug-drug interaction study with eribulin and a CYP3A4 inducer (rifampicin) is ongoing.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical studies addressing the mechanism of action were submitted.

Primary and Secondary pharmacology

Primary pharmacology

Tumour responses have been seen in phase–I studies of advanced solid tumours which primarily aimed at determining the MTD of eribulin (data not shown).

Biomarkers for resistance

Eribulin has showed *in vitro* activity against cancer cells that are taxane-resistant due to ß-tubulin mutations. A phase-I study (NCI-5730) and a phase-II study (Study 201) in the present application studied the effects of class III ß-tubulin mutations however both provided preliminary evidence to suggest that the expression of ßIII-tubulin impacted eribulin efficacy in a similar manner as it impacts the efficacy of taxanes.

Secondary pharmacology

Exposure-response

Exposure-adverse event analyses were performed and models describing the probability of fatigue, neuropathy and neutropenia were developed.

Exposure of eribulin (dose, Cmax or AUC) was not identified as a significant predictor of the probability of fatigue, but the best predictor was stratified Eastern Cooperative Oncology Group (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.

The best model describing the probability of neuropathy used AUC multiplied by cycle number to predict the likelihood of neuropathy, in line with that development of neuropathy is cumulative. Finally, the probability of a patient experiencing a Grade 4 neutropenia was estimated to be dependent on eribulin exposure (AUC) and AST. The effect of AST in addition to systemic exposure was unexpected and there is no evident mechanistic reason.

QT study

The study 110 was undertaken in 26 patients without a positive control. QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. As eribulin is a cytotoxic drug, the study was not optimal to exclude such effects and a warning was included in section 4.4 of the SmPC.

2.4.4. Discussion and conclusions on clinical pharmacology

There are no issues raised concerning the human pharmacokinetic part of the documentation. However, the applicant has been requested, as part of the risk management plan, to try to identify the main transporters involved in the biliary excretion (main elimination pathway) of eribulin to allow predictions of potential drug interactions at transporter level (see section 2.7).

The effect of hepatic impairment has been investigated in patients with impairment due to metastases. This is likely the most common cause of hepatic impairment in the population. Dosing adjustments are proposed based on Child Pugh classification.

The exposure is markedly increased in hepatic impairment (2- and 3-fold in mild and moderate impairment respectively). There are no data in severe hepatic impairment but it may be expected that the exposure is even further increased. However, it is considered unlikely that patients with severe impairment due to metastases will be treated with eribulin and the lack of data is therefore not considered an issue to follow up further. The applicant should propose recommendations for patients with hepatic impairment due to cirrhosis. Furthermore, the applicant should investigate whether, based on the hepatic impairment study data, any of the clin. chem. markers within the Child Pugh classification may be used for dose adjustment. This information is currently reflected in the RMP (see section 2.7). In the mean time, patients with mild and moderate hepatic impairment should reduce the dose of eribulin to 0.97 mg/m^2 and 0.62 mg/m^2 respectively. Severe hepatic impairment has not been studied but it is expected that a more marked dose reduction is needed if eribulin is used in these patients. Although patients with impaired liver function due to cirrhosis have not been studied, the doses above may be used in mild and moderate impairment. These patients will have to be closely monitored as the doses may need readjustment.

The effect of ethnicity was not studied in specific pharmacokinetic studies. An assessment was included in the population PK analysis and no effect was identified. However, definite conclusions concerning ethnicity cannot be made on the basis of the population PK analysis since the main part were Caucasian subjects and one portion of the patients had unknown ethnicity.

Eribulin is mainly eliminated through biliary excretion (up to 70%). Thus, the major source of interactions affecting the pharmacokinetics of eribulin will be caused by inhibition or induction of the involved transporters which are unknown.

Eribulin should not be used concomitantly with inhibitors of hepatic transport proteins such as organic anion-transporting proteins (OATPs), P-glycoprotein (P-gp), multidrug resistant proteins (MRPs) as described in section 4.5 of the SmPC.

The applicant will investigate which transporter is involved to allow predictions of potential drug interactions at transporter level. While this is investigated, the applicant will include a list of potent inhibitors of hepatic uptake and efflux transporters in the SmPC and propose adequate practically applicable treatment recommendations for situations where concomitant treatment is needed. These additional investigations regarding transporters are addressed in the RMP (see section 2.7).

Preclinical studies suggest that P-gp can transport eribulin.

An interaction study with ketoconazole showed no effect on eribulin exposure. Available results indicate that ketoconazole inhibits P-gp but interaction studies with P-gp probe substrates are lacking. Thus the lack of interaction cannot be extrapolated to potent P-gp inhibitors (see SmPC section 4.5). The applicant will therefore present *in vivo* data supporting ketoconazole as a P-gp inhibitor and discuss whether ketoconazole is less potent that the CYP3A4 inhibitors used in the clinical studies as described in the RMP (see section 2.7).

Concomitant treatment with enzyme inducing drugs such as rifampicin, carbamazepine, phenytoin, St John´s wort (Hypericum perforatum) is not recommended as these drugs are likely to give rise to markedly reduced plasma concentrations of eribulin.

No drug-drug interactions are expected with CYP3A4 inhibitors unless they are potent inhibitors of P-gp. Eribulin exposure (AUC and C_{max}) was unaffected by ketoconazole, a CYP3A4 inhibitor.

Eribulin may inhibit the important drug metabolising enzyme CYP3A4. This is indicated by *in vitro* data and no *in vivo* data is available. Concomitant use with drugs that are mainly metabolised by CYP3A4 should be made with caution and it is recommended that the patient is closely monitored for adverse effects due to increased plasma concentrations of the concomitantly used drug. If the drug has a narrow therapeutic range, concomitant use should be avoided. Eribulin does not inhibit the CYP enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at relevant clinical concentrations.

CYP2C19 is not induced by eribulin. This provides some support for lack of Pregnane X receptor (PXR) mediated induction by eribulin but no definitive conclusions can be drawn. No further induction studies are required, however, the applicant is encouraged to investigate this further.

2.5. Clinical efficacy

2.5.1. Dose response studies

The phase I program consisted of:

- one National Institute of Health (NIH)-sponsored study, NCI-5730, and
- two studies sponsored by the applicant, Study 101 and Study 102.

A total of 94 patients with refractory or advanced solid tumours were enrolled in these three studies. The NCI-5730 study and Study 101 both used a dosing regimen of Days 1, 8, and 15 every 28 days, and the MTD in these studies was determined to be 1.4 mg/m^2 and 1.0 mg/m^2 (as eribulin mesylate)

respectively. Study 102 used a dosing schedule of Day 1 every 21 days, and the MTD was determined to be 2.0 mg/m^2 as eribulin mesylate.

The dosing regimen of the pivotal study (1.23 mg/m^2 eribulin on Days 1 and 8 of a 21-day cycle) was selected based on results of two completed phase II studies (Study 201 and 202)which were both initiated with a dosing regimen of 1.23 mg/m^2 eribulin on Days 1, 8 and 15 every 28 days. A second cohort of patients was added to both these studies to evaluate the 21-day dosing regimen. In the breast cancer study 201(n= 103 in full ITT population) the 21-day regimen showed numerically better results with regard to ORR, PFS and OS along with better tolerability. Another phase II-study in breast cancer (Study 211, n=291 in ITT population) was then undertaken which also showed acceptable tolerability of the 21-day dosing regimen. (Efficacy results for studies 201 and 211 are shown in Table 15 under Supportive studies).

2.5.2. Main study

E7389-G000-305: a phase III open label, randomised parallel two-arm multi centre study of eribulin versus "Treatment of Physician's Choice" (TPC) in patients with locally recurrent or metastatic breast cancer, previously treated with at least two and a maximum of five prior chemotherapy regimens, including an anthracycline and a taxane.

Acronym: The **EMBRACE** trial: **E**isai **M**etastatic **Br**east Cancer Study **A**ssessing Physician's **C**hoice Versus **E**7389.

Methods

Study Participants

Inclusion Criteria

1. Female patients with histologically or cytologically confirmed carcinoma of the breast.
2. Patients with locally recurrent or metastatic disease who had received at least 2 (and not more than 5) prior chemotherapeutic regimens for breast cancer, at least 2 of which were administered for treatment of locally recurrent and/or metastatic disease. Prior therapy had to include an anthracycline and a taxane in any combination or order (unless contraindicated for a certain patient). Prior trastuzumab and anti-hormonal therapy was allowed.
3. Patients have proved refractory to the most recent chemotherapy, documented by progression on or within six months of therapy.
4. Resolution of all prior chemotherapy or radiation-related toxicities to Grade 1 severity or lower, except for stable sensory neuropathy ≤ Grade 2 and alopecia.
5. Age ≥18 years.
6. Performance Status of 0 to 2 according to Eastern Cooperative Oncology Group (ECOG)/WHO.
7. Life expectancy of ≥3 months.
8. Adequate renal, bone-marrow, and liver function as evidenced by serum laboratory values.
9. Written informed consent, and patient able to comply with study protocol.

Exclusion criteria:

1. Patients who had received any of the following treatments within the specified period before eribulin or TPC treatment start:
    - chemotherapy, radiation, trastuzumab or hormonal therapy within three weeks.
    - any investigational drug within four weeks.
2. Radiation therapy encompassing >30% of marrow.
3. Prior treatment with mitomycin C or nitrosourea.
4. Pulmonary lymphangitic involvement causing pulmonary dysfunction requiring active treatment, including the use of oxygen.
5. Brain or subdural metastases, unless local therapy completed and the use of corticosteroids discontinued for this indication for at least four weeks before starting treatment in this study. Radiologic investigations and symptoms of brain metastases had to be stable for at least four weeks before starting study treatment.
6. Meningeal carcinomatosis.
7. Anti-coagulant therapy with warfarin or related compounds, other than for line patency. Mini-dose warfarin could be allowed if closely monitored.
8. Women who were pregnant or breast-feeding; women of childbearing potential unless (1) surgically sterile or (2) using adequate measures of contraception in the opinion of the Investigator.
9. Severe/uncontrolled intercurrent illness/infection, or other significant disease or disorder that, in the Investigator's opinion, excluded the patient from the study.
10. Significant cardiovascular impairment, including serious cardiac arrhythmia, unstable angina or myocardial infarction within the previous 6 months.
11. Organ allografts requiring immunosuppression.
12. Known positive Human Immunodeficiency Virus status.
13. Prior malignancy, other than previous breast cancer, carcinoma in situ of the cervix, or non-melanoma skin cancer, unless the prior malignancy was diagnosed and definitively treated ≥5 years previously with no subsequent evidence of recurrence.
14. Pre-existing neuropathy > Grade 2.
15. Hypersensitivity to Halichondrin B and/or Halichondrin B chemical derivative.
16. Participation in a prior eribulin clinical study.

Treatments

Patients were randomised 2:1 to receive the investigational drug eribulin mesylate (eribulin) or TPC.

Eribulin was administered as an IV bolus at 1.23 mg/m^2 over two to five minutes, on Days 1 and 8 of a 21-day cycle.

The 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 local practice, if applicable. The use of other investigational drugs, or products not registered for the treatment of cancer was not allowed.

Objectives and endpoints

The objectives, endpoints and their definitions are shown in Table 4.

Table 4. Objectives and endpoints

Primary objective	Primary endpoint and definition
1. To compare the overall survival of patients treated with eribulin versus TPC.	**Overall survival (OS),** defined as the time from the date of randomization until death from any cause. 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 (12 May 2009) were censored at the date last known alive. Patients who were alive on the data cut-off date were censored at the data cut-off date for OS analyses.
Secondary objectives	**Secondary endpoints and definitions**
2. To compare progression-free survival between the two treatment groups.	**Progression-Free Survival (PFS)**, defined as the time from the date of randomization until PD (by clinical evaluation or as documented by RECIST criteria from *Independent review, see below*) or death from any cause in the absence of disease progression. Patients who were alive and progression-free on the data cut-off date were censored at the data cut-off date.
3. To assess objective tumour response rate as measured using "Response Evaluation Criteria in Solid Tumors" (RECIST) criteria.	**Objective tumour Response Rate (ORR)**, defined as the number of patients with a *confirmed (see below)* CR or *confirmed* PR divided by the number of patients in the analysis population. The response rate was based on the *Independent review* of disease assessments. Subjects with unknown or missing response were treated as non-responders.
4. To compare the duration of response in each treatment group.	**Duration of Response (DoR)**, defined as the time from first documented evidence of complete response (CR) or partial response (PR) (whichever status is recorded first) until the first documented sign of disease progression or death due to any cause. For patients in the subset of responders who did not progress or die, duration of response was censored. Response was derived from the *Independent review* of best response. A sensitivity analysis was also conducted based on the investigator's disease assessments.
5. To collect and investigate safety parameters for all patients.	Frequency and severity of Adverse Events (AEs), laboratory measurements, concomitant medication, and study drug exposure.

Tumour assessments were performed according to RECIST criteria using Magnetic resonance imaging (MRI) or spiral/multidetector Computed tomography with IV or oral contrast, as appropriate. Ultrasound was not to be used. Superficial lesions were measured with calliper and/or ruler, and documented by photography including a ruler. If a lesion was assessable by both radiological and clinical techniques, radiological techniques were to be used. The same imaging/assessment modality was to be used on measurable disease at all time points. The tumour response was analysed according to a) *Investigator assessment*, and b) *Independent revi*ew blinded to patient ID and allocated treatment. The latter was used for the primary analyses of the secondary endpoints PFS and tumour response.

A maximum of 10 target lesions were selected to be measured (maximum 5 from each tumour site). All other lesions were defined as non-target lesions, and were followed only as "present" or "absent".

Response assessments were performed every 8 weeks (+/- 1 week), or sooner if suspicion of disease progression.

Confirmation of tumour response (CR or PR) was to be performed by a second examination no less than four weeks after first observation of response. Only confirmed responses were considered CR or PR for the best response and included in the ORR.

Sample size

A total of 762 patients were randomised in a 2:1 ratio to receive eribulin or TPC. Initially a lower number of 630 patients (420 in eribulin and 210 in TPC) were planned, but this was amended following a pre-planned evaluation of the event rate (pre-specified in the protocol), 15 months after the first patient was recruited (January 2008). The primary analysis was thus planned to occur when 411 events (deaths) had been recorded in 630 patients, leading to an initial estimated maximum study duration of 26.5 months. The pooled event rate evaluation suggested that the number of events was smaller than expected, and therefore a decision was made to increase the sample size to allow up to a maximum of 1000 patients in order to achieve the required number of deaths sooner. 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. These sample size re-assessments were conducted in-house by a statistician who was blinded to treatment assignment. The pooled event rate was communicated to the immediate study management team for decision making purposes. The study team did not have access to the relative efficacy data per treatment arm.

Randomisation

Patients were randomised in a 2:1 ratio to receive either eribulin or TPC.

Stratification:

Patients were pre-stratified based on the following three factors:

1. Geographic regions: Region 1: North America/Western Europe/Australia (i.e. Australia, Belgium, Canada, France, Germany, Italy, Spain, Switzerland, the UK, and the USA.)

   Region 2: Eastern Europe (i.e. Croatia, the Czech Republic, Hungary, Poland, Russia and Turkey.)

   Region 3: Latin America/South Africa (i.e. Argentina, Brazil and South Africa.)

2. HER2/neu status: positive / negative / unknown

3. Prior treatment with capecitabine: yes / no

Randomisation procedure:

Prior to randomisation (and after evaluation for eligibility), the proposed TPC agent that would have been given if the patient was 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 randomised to eribulin or TPC treatment within each stratum in a 2:1 ratio (eribulin to TPC). Treatment allocation and a randomization number were given for each patient.

Blinding (masking)

The study was an open label study. However, the sponsor study team was blinded for OS data until database lock to avoid potential bias. Independent statisticians conducted the interim analysis, and assisted with queries surrounding all death events. An independent data monitoring committee was

used to review the safety of eribulin treatment in the study and to assess interim efficacy data to determine whether the study should continue as planned. The sponsor study team did not have access to the interim data.

Statistical methods

Primary endpoint, OS

Primary analysis: OS in ITT population, using a two-sided stratified log-rank test at a significance level of 0.049 (adjusted for the interim analysis). The ITT population was defined as patients who were randomised irrespective of whether or not they actually received the treatment they were randomised to. The PP population included all patients in the ITT population who met the major inclusion criteria and who did not have any major protocol violation.

Results

Participant flow

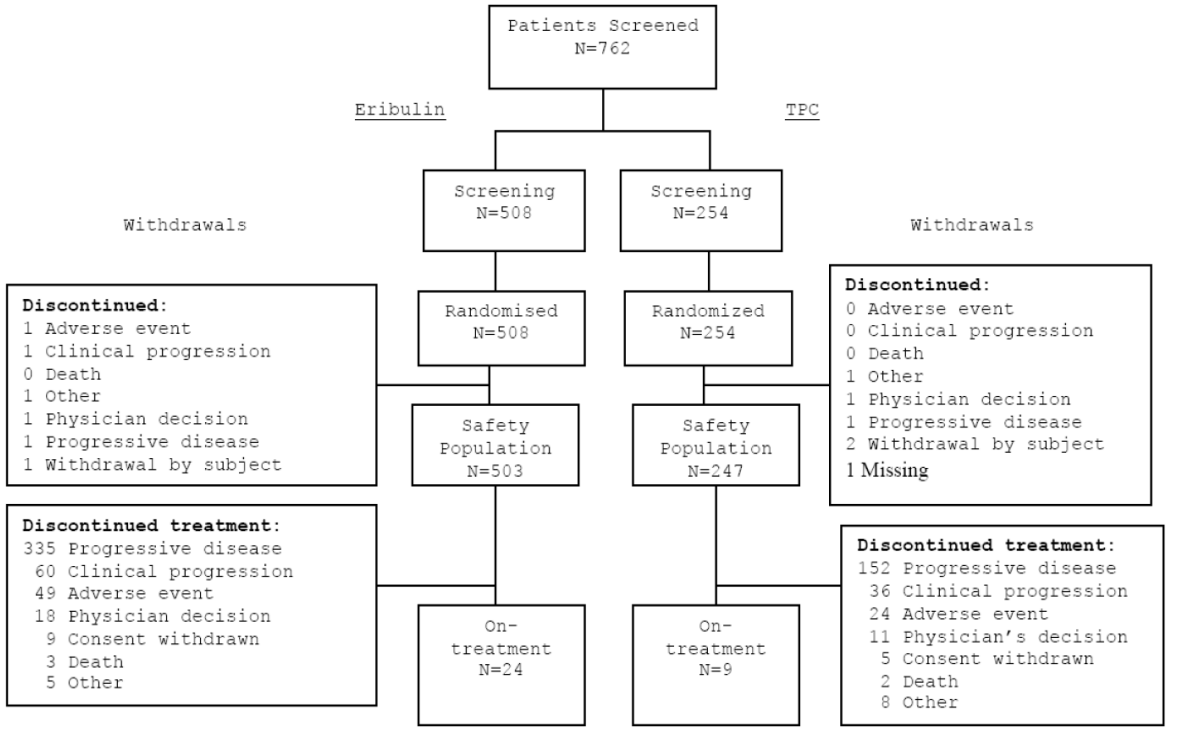


Figure 1. Study flowchart

Table 5. Recruitment

First patient entered the study	16 November 2006
Date of last enrolment	in November 2008
1st Data cut-off:	12 May 2009
Updated overall survival analysis	
Data cut-off:	3 March 2010

Conduct of the study

Study 305 was conducted in 135 centres in 19 countries: Argentina, Australia, Belgium, Brazil, Canada, Croatia, Czech Republic, France, Germany, Hungary, Italy, Poland, Russia, South Africa, Spain, Switzerland, Turkey, United Kingdom, and the United States.

The TPC arm consisted of 97% chemotherapy (26% vinorelbine, 18% gemcitabine, 18% capecitabine, 16% taxane, 9% anthracycline, 10% other chemotherapy), or 3% hormonal therapy.

Protocol amendments

The original study protocol was issued on April 26, 2006. Four amendments were made to the protocol, and a final protocol was produced on March 03, 2009. The first amendment was made before first patient in, November 16, 2006. Major amendments are listed below.

Amendment 1 (8 August 2006):

Reasons for Amendments: Incorporating scientific advice from EMEA and updating administrative changes.

- Added as inclusion criterion that patients must have proved refractory to the most recent chemotherapy, documented by progression on or within six months of therapy.
- Allowed patients without measurable disease to be enrolled since the primary objective was OS.
- Amended stratifications factors to include prior capecitabine.

Amendment 2 (4 January 2008):

- Allowed patients who commenced bisphosphonates after starting study treatment to continue in the study on agreement with the sponsor.
- Changed the Eligible Population to the PP Population, to allow inclusion of patients that did not have major protocol violations in the PP Population.

Amendment 3 (5 June 2008):

- Increased population size to approximately 1000 patients in order to achieve the number of events required for the primary analysis sooner.

Protocol deviations

Forty-four of the patients (8.7%) in the eribulin group and 33 patients (13.0%) in the TPC group were excluded from the PP population due to deviations from inclusion/exclusion criteria.

The most frequently observed deviations from the inclusion/exclusion criteria concerned the patient not being refractory to the most recent chemotherapy, occurring in 16 (3.1%) in the eribulin group and 11 (4.3%) in the TPC group; followed by having received more than five prior chemotherapy regimens in 15 (3.0%) patients in the eribulin group and 9 (3.5%) patients in the TPC group; and the patient having received only one regimen for locally recurrent or metastatic disease in 7 (1.4%) patients in the eribulin group and 8(3.1%) in the TPC group. An additional 10 patients were excluded from the PP population because they did not receive study treatment.

Protocol deviations that did not cause exclusion from the PP population included among others: randomised with brain metastasis, concomitant treatment with anti-hormonal agents, bisphosphonates

or warfarin, error in BSA calculation leading to patient being underdosed, and patient receiving study drug after disease progression.

Baseline data

For demographics refer to table 5 for important baseline patient and tumour characteristics see table 6 and for prior anti-cancer therapy table 7.

Table 5: Patients' demography

	Treatment Group		Total
	Eribulin N = 508	TPC N = 254	N = 762
Age (years)			
N	508	254	762
Mean (sd)	54.8 (10.34)	55.9 (10.43)	55.2 (10.37)
Median	55.0	56.0	55.0
Minimum, Maximum	28, 85	27, 81	27, 85
Age distribution, n (%)			
<40 years	34 (6.7)	17 (6.7)	51 (6.7)
≥40 to <65 years	380 (74.8)	180 (70.9)	560 (73.5)
≥65 years	94 (18.5)	57 (22.4)	151 (19.8)
Sex, n (%)			
Female	508 (100.0)	254 (100.0)	762 (100.0)
Race, n (%)			
Black	20 (3.9)	14 (5.5)	34 (4.5)
White	470 (92.5)	233 (91.7)	703 (92.3)
Asian/Pacific Islander	3 (0.6)	2 (0.8)	5 (0.7)
Other	15 (3.0)	5 (2.0)	20 (2.6)
Height (cm)			
N	497	252	749
Mean (sd)	161.9 (6.64)	161.0 (6.74)	161.6 (6.68)
Median	162.0	162.0	162.0
Minimum, Maximum	142, 179	141, 183	141, 183
Geographical region, n (%)			
North America/Western Europe/ Australia	325 (64.0)	163 (64.2)	488 (64.0)
Eastern Europe	129 (25.4)	64 (25.2)	193 (25.3)
Latin America /South Africa	54 (10.6)	27 (10.6)	81 (10.6)
Reproductive status n (%)			
Fertile	46 (9.1)	20 (7.9)	66 (8.7)
Post-menopausal	379 (74.6)	199 (78.3)	578 (75.9)
Surgically sterile	78 (15.4)	35 (13.8)	113 (14.8)
Infertile	5 (1.0)	0	5 (0.7)

Abbreviations: ITT = Intent-to-treat; sd = Standard deviation; TPC = Treatment of Physician's Choice.

Table 6: Summary of Selected Baseline Characteristics (ITT Population: Study 305)

Parameter	Treatment Group		Total
	Eribulin N = 508 n (%)	TPC N = 254 n (%)	N = 762 n (%)
Time since original diagnosis (years)			
Mean (sd)	6.7 (4.98)	6.6 (4.95)	6.7 (4.96)
Median	5.4	5.1	5.2
Min, Max	0.1, 37.4	0.6, 22.9	0.1[e], 37.4
Tumour sites in >10% patients overall, n (%)			
Bone	306 (60.2)	158 (62.2)	464 (60.9)
Liver	296 (58.3)	159 (62.6)	455 (59.7)
Lymph nodes	220 (43.3)	118 (46.5)	338 (44.4)
Lung	197 (38.8)	95 (37.4)	292 (38.3)
Pleura	87 (17.1)	42 (16.5)	129 (16.9)
Breast	54 (10.6)	24 (9.4)	78 (10.2)
Number of organs involved, n (%)[a]			
1	85 (16.7)	35 (13.8)	120 (15.7)
2	172 (33.9)	82 (32.3)	254 (33.3)
3	145 (28.5)	77 (30.3)	222 (29.1)
4	71 (14.0)	37 (14.6)	108 (14.2)
5	24 (4.7)	16 (6.3)	40 (5.2)
≥6	9 (1.8)	7 (2.8)	16 (2.1)
HER2/*neu* status (combined FISH and IHC tests), n (%)[b]			
Positive	83 (18.0)	40 (17.2)	123 (17.8)
Negative	373 (81.1)	192 (82.8)	565 (81.6)
Unknown	4 (0.9)	0	4 (0.6)
Not done	48	22	70
ER status, n (%)[b]			
Positive	336 (70.0)	171 (70.4)	507 (70.1)
Negative	143 (29.8)	72 (29.6)	215 (29.7)
Unknown	1 (0.2)	0	1 (0.1)
Not done	28	11	39
PgR status, n (%)[b]			
Positive	254 (56.2)	123 (54.7)	377 (55.7)
Negative	197 (43.6)	102 (45.3)	299 (44.2)
Unknown	1 (0.2)	0	1 (0.1)
Not done	56	29	85
Negative for ER, PgR and HER2/*neu*, n (%)[b]			
Yes	93 (18.3)	51 (20.9)	144 (19.8)
No	380 (78.8)	192 (78.7)	572 (78.8)
Unknown[c]	9 (1.9)	1 (0.4)	10 (1.4)
ECOG performance status, n (%)			
0	217 (42.7)	103 (40.6)	320 (42.0)
1	244 (48.0)	126 (49.6)	370 (48.6)
2	39 (7.7)	22 (8.7)	61 (8.0)
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)

Abbreviation: ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; FISH = fluorescence in-situ

Parameter	Treatment Group		Total
	Eribulin N = 508 n (%)	TPC N = 254 n (%)	N = 762 n (%)

hybridization; HER2/*neu* = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ITT = intent-to-treat; max = maximum; min = minimum; PgR = progesterone receptor; sd = standard deviation; TPC = Treatment of Physician's Choice.

[b] The number of organs involved is based on the Investigator review data.

[c] For the HER2, ER, PgR, and triple negative status, the percentages are calculated from the total number of patients tested.

[d] Unknown includes the patients who were ER and PgR negative, for whom the results of HER2 testing were unknown

Note: for baseline characteristics relating to disease locations, Independent data were used except where noted.

Table 7: Prior Anti-Cancer Therapy (ITT Population)

Parameter	Treatment Group		Total
	Eribulin N = 508	TPC N = 254	N = 762
Number of prior chemotherapy regimens, n (%)			
1	1 (0.2)	0	1 (0.1)
2	65 (12.8)	31 (12.2)	96 (12.6)
3	176 (34.6)	83 (32.7)	259 (34.0)
4	166 (32.7)	79 (31.1)	245 (32.2)
5	85 (16.7)	51 (20.1)	136 (17.8)
≥6	13 (2.6)	9 (3.5)	22 (2.9)
Duration of last chemotherapy (months)			
Median (Minimum, Maximum)[a]	3.57 (0.0, 32.0)	3.50 (0.1, 25.3)	3.53 (0.0, 32.0)
Number of patients who previously received: n (%)			
Taxanes	503 (99.0)	251 (98.8)	754 (99.0)
Anthracyclines	502 (98.8)	250 (98.4)	752 (98.7)
Capecitabine	370 (72.8)	189 (74.4)	559 (73.4)
Number of prior hormonal regimens, n (%)			
1	220 (43.3)	96 (37.8)	316 (41.5)
2	109 (21.5)	65 (25.6)	174 (22.8)
3	60 (11.8)	23 (9.1)	83 (10.9)
4	28 (5.5)	21 (8.3)	49 (6.4)
5	10 (2.0)	1 (0.4)	11 (1.4)
≥6	3 (0.6)	4 (1.6)	7 (0.9)
Number of patients refractory[b] to: n, (%)			
Taxane	410 (80.7)	204 (80.3)	614 (80.6)
Capecitabine	342 (67.3)	174 (68.5)	516 (67.7)
Anthracycline	284 (55.9)	156 (61.4)	440 (57.7)
Prior radiotherapy, n (%)			
Yes	420 (82.7)	195 (76.8)	615 (80.7)
No	88 (17.3)	59 (23.2)	147 (19.3)

Abbreviations: ITT = Intent-to-treat; TPC = Treatment of Physician's Choice.
a: Patients with a zero duration of last chemotherapy were patients who received only a single dose of the last chemotherapy agent that they were receiving prior to starting on study.
b: Refractory was defined as progressed within six months of receiving the therapy.

Numbers analysed

One patient received eribulin instead of TPC, which she was randomised to, and was included in the TPC group in the ITT population, excluded from the PP population, and included in the eribulin group in the safety population. The ITT population for study 305 was 762 patients in total (Eribulin n=508 and TPC n=254) and the PP population was 675 in total (Eribulin n=459 and TPC n=216).

Outcomes and estimation

Overall Survival and Progression Free Survival – initial primary analysis

Table 8: Summary of efficacy endpoints in pivotal Study 305

Variable	OS/ITT		OS/PP		PFS/ITT Independent review		PFS/ITT Investigator Assessment	
	Eribulin	TPC	Eribulin	TPC	Eribulin	TPC	Eribulin	TPC
n	508	254	459	216	508	254	508	254
Events n (%)	274 (54)	148 (58)	244 (53)	123 (57)	357 (70)	164 (65)	429 (84)	206 (81)
Median (days) 95% CI	399 (360, 434)	324 (282, 380)	403 (365, 446)	326 (286, 433)	113 (101, 118)	68 (63, 103)	110 (100, 114)	66 (60, 79)
1-year rate (%)	54	44	55	45	9	7	7	7
P-value [a]	0.041		0.066		0.137		0.002	
HR [b] (95%CI)	0.809 (0.660, 0.991)		0.812 (0.650, 1.015)		0.865 (0.714, 1.048)		0.757 (0.638, 0.900)	
HR incl. number of prior CT [c] (95%CI)	0.810 (0.660, 0.994)		0.813 (0.650, 1.018)		-		-	

CT = chemotherapy regimens
a: Stratified log-rank test. Significance level in primary analysis of primary objective (OS/ITT) was 0.049, adjusted for interim analysis.
b: Hazard ratio based on a Cox model including HER2/neu status, prior capecitabine treatment, and geographical region as strata.
c: Hazard ratio based on a Cox model including HER2/neu status, prior capecitabine treatment, geographical region as strata, and number of prior chemotherapy regimens, and oestrogen receptor status as covariates.

Table 9. Summary of Concordance of Progression Data

Treatment Group			**Independent Review, n (%)**	
			PD	**No PD**
Overall (N=762)	**Investigator Review**	**PD**	496 (65.1)	139 (18.2)
		No PD	25 (3.3)	102 (13.4)
Eribulin (N=508)	**Investigator Review**	**PD**	338 (66.5)	91 (17.9)
		No PD	19 (3.7)	60 (11.8)
TPC (N=254)	**Investigator Review**	**PD**	158 (62.2)	48 (18.9)
		No PD	6 (2.4)	42 (16.5)

PD = progressive disease, TPC = treatment of physician's choice.

Updated Overall Survival data (data cut-off: 3 March 2010)

Table 10. Original and Updated Kaplan-Meier Analyses of Overall Survival (ITT Population)

Analysis and cut-off date	Original analysis 12 may 2009		Updated analysis 03 March 2010	
Treatment group	Eribulin	TPC	Eribulin	TPC
n	508	254	508	254
Events n (%)	274 (54)	148 (58)	386 (76)	203 (80)
Median (days) 95% CI	399 (360, 434)	324 (282, 380)	403 (367, 438)	321 (281, 365)
1-year rate (%)	54	44	55	43
2-year rate (%)	22	27	22	19
P-value [a]	0.041		0.014	
HR [b] (95%CI)	0.809 (0.660, 0.991)		0.805 (0.677, 0.958)	
HR incl. number of prior CT [c] (95%CI)	0.810 (0.660, 0.994)		0.809 (0.680, 0.963)	

CT = chemotherapy regimens. a: Stratified log-rank test. Significance level in primary analysis of primary objective (OS/ITT) was 0.049, adjusted for interim analysis. b: Primary analysis: hazard ratio based on a Cox model including HER2/neu status, prior capecitabine treatment, and geographical region as strata. c: Sensitivity analysis: hazard ratio based on a Cox model including HER2/neu status, prior capecitabine treatment, geographical region as strata, and number of prior chemotherapy regimens, and oestrogen receptor status as covariates.

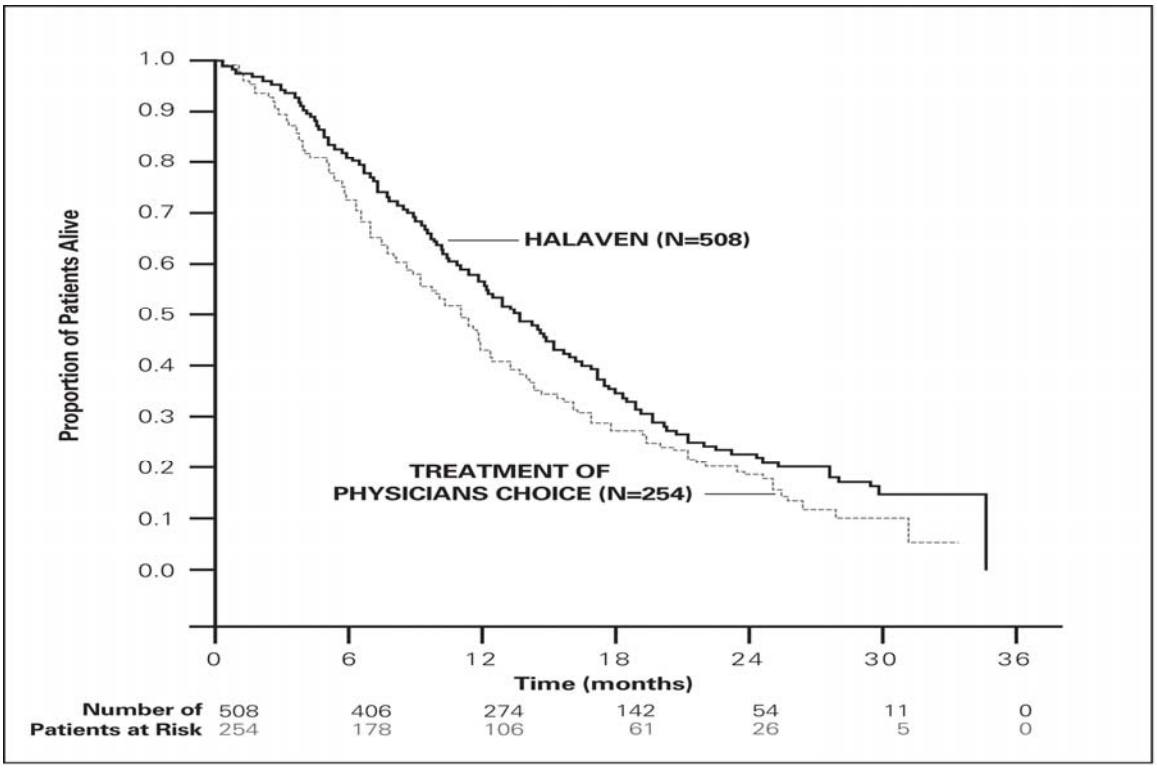


Figure 2. Kaplan-Meier Analysis of Overall Survival update data (ITT Population)

Objective response rate

Table 11. Best Overall Response as Assessed by Investigator Review and Independent Review (Response Evaluable Population)

Response Category	Treatment Group			
	Independent Review		Investigator Review	
	Eribulin N = 468 n (%)	TPC N = 214 n (%)	Eribulin N = 468 n (%)	TPC N = 214 n (%)
CR	3 (0.6)	0	1 (0.2)	0
PR	54 (11.5)	10 (4.7)	61 (13.0)	16 (7.5)
SD	208 (44.4)	96 (44.9)	219 (46.8)	96 (44.9)
PD	190 (40.6)	105 (49.1)	176 (37.6)	97 (45.3)
Not Evaluable	12 (2.6)	3 (1.4)	11 (2.4)	5 (2.3)
Unknown	1 (0.2)	0	0	0
Objective Response Rate (CR+PR)	**57 (12.2)**	**10 (4.7)**	**62 (13.2)**	**16 (7.5)**
95% CI[a]	(9.4, 15.5)	(2.3, 8.4)	(10.3, 16.7)	(4.3, 11.9)
p-value[b]	0.002		0.028	
Clinical Benefit Rate (CR+PR+SD≥6 months)[c]	**106 (22.6)**	**36 (16.8)**	**130 (27.8)**	**43 (20.1)**
95% CI[a]	(18.9, 26.7)	(12.1, 22.5)	(23.8, 32.1)	(14.9, 26.1)

Abbreviations: CI = confidence interval; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; TPC = Treatment of Physician's Choice. a: Exact Pearson-Clopper two-sided CI, b: Fisher's Exact Test c: Clinical Benefit = CR or PR, or SD of at least six month duration.

Duration of response

The median response duration in this population by independent review was 128 days (95% CI: 116, 152 days). The median response duration was 145 days (95% CI: 124, 190 days) according to Investigator assessment.

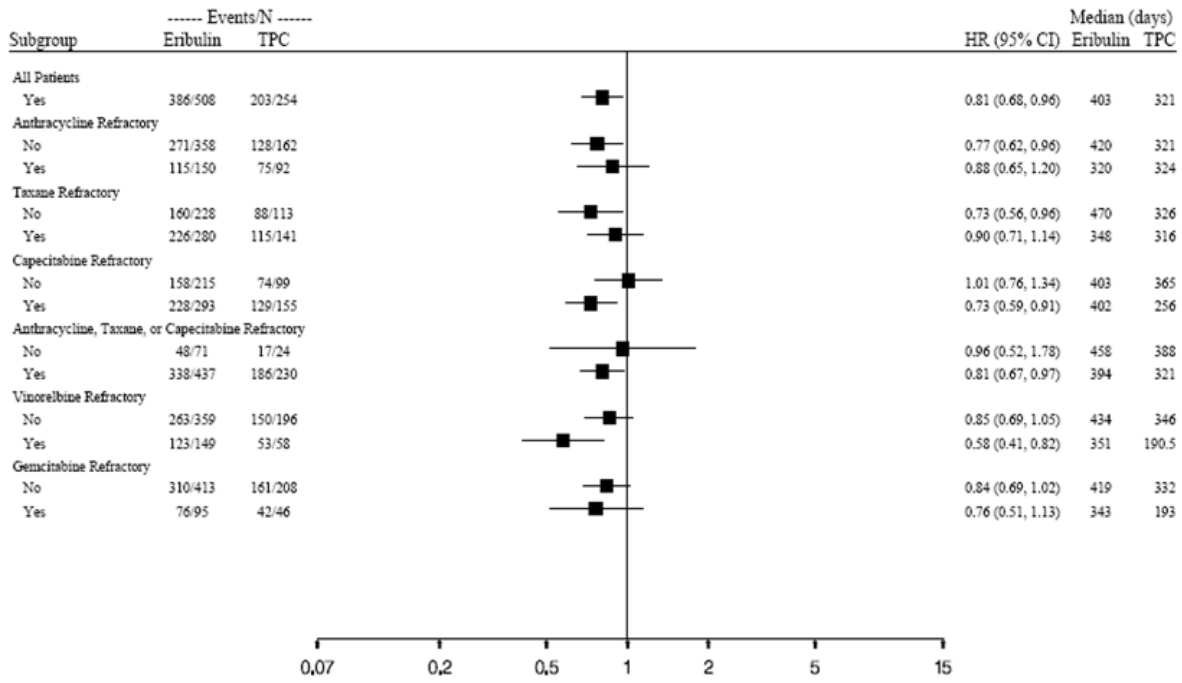
Ancillary analyses

Taxane-refractory vs. non-refractory patients

The original analysis of the effect of eribulin in relation to type and refractoriness of prior lines of therapy revealed that patients refractory (defined as progression within 2 months of therapy) to prior taxane treatment had no discernible advantage of eribulin compared with TPC with regard to OS, HR: 0.98 (95% CI 0.74, 1.30), whereas patients not refractory to taxanes had a clear statistically significant benefit of eribulin over TPC, HR: 0.63 (95% CI 0.46, 0.87).

For the other tubulin-targeting drug used, vinorelbine, a better HR of 0.56 (95% CI 0.38, 0.83) was seen for refractory patients compared with patients not refractory to vinorelbine, HR 0.86 (95% CI 0.68, 1.10).

In the updated OS analysis, the HR for eribulin vs. TPC in the taxane-refractory patients (defined as progression within 60 days of taxane therapy) has decreased compared with the original analysis, from 0.98 (95% CI 0.74, 1.30) to 0.90 (95% CI 0.71, 1.14). At the same time the HR in the taxane non-refractory group has increased from 0.63 (95% CI 0.0.46, 0.87) to 0.73 (95% CI 0.56, 0.96), and the point estimates from both groups are within the CI of the other (see figure 3). In the Investigator assessment-based analysis of PFS (based on original data cut-off), the HR was 0.77 (95% CI 0.61, 0.97) for taxane-refractory patients and 0.76 (95% CI 0.58, 0.99) for patients not taxane-refractory.



Note: Hazard ratio is calculated with TPC as the reference group based on stratified Cox regression adjusted for HER2/*neu* status, prior capecitabine treatment and geographical region as strata.
Note: All prior episodes of chemotherapy were considered, including therapies for neo-adjuvant, adjuvant and metastatic disease. For missing dates where timing could not be determined these were considered as nonrefractory.
Note: A smaller hazard ratio is in favour of eribulin.
CI = confidence interval; HER2/*neu* = human epidermal growth factor receptor 2, HR = hazard ratio, ITT = intent-to-treat, TPC = treatment of physician's choice.

Figure 3: Treatment Comparison of Overall Survival (OS Update) by Chemotherapy Refractoriness (ITT population: Study 305) (Patients that Progressed Within 60 Days of Last Therapy)

Table 12: Kaplan-Meier Analysis of Progression-Free Survival by Investigator Review According to Taxane Refractory Subgroups (ITT Population)

	Taxane refractory		**Taxane non-refractory**	
6 month definition of refractory	**Eribulin Arm (n=374)**	**TPC Arm (n=191)**	**Eribulin Arm (n=134)**	**TPC Arm (n=63)**
PFS, days				
Median	106	62	125	84
(95% CI for median)	79, 112	58, 71	107, 169	63, 128
Hazard ratio (eribulin/TPC)[a]				
Estimate (95% CI)	0.770 (0.632, 0.938)		0.761 (0.533, 1.088)	
60 day definition of refractory	**Eribulin Arm (n=280)**	**TPC Arm (n=141)**	**Eribulin Arm (n=228)**	**TPC Arm (n=113)**
PFS, days				
Median	106	60	113	71
(95% CI for median)	84, 114	57, 71	100, 129	64, 113
Hazard ratio eribulin/TPC)[a]				
Estimate (95% CI)	0.768 (0.609, 0.967)		0.758 (0.583, 0.986)	

CI = confidence interval, ITT = intent-to-treat, PFS = progression-free survival, TPC = treatment of physician's choice.
Note: Refractory to a medication was defined as the patient had a disease progression within 6 months or 60 days after taking the last dose of the medication.
a: Hazard ratio based on a Cox model including HER2/*neu* status, prior capecitabine treatment and geographical region as strata.

Capecitabine-naive versus capecitabine pre-treated patients

In the initial OS/ITT analysis, patients refractory to capecitabine showed a statistically significant HR of 0.68 (95% CI 0.53, 0.88) for eribulin vs. TPC, whereas in patients not refractory to capecitabine no advantage for eribulin over TPC was seen, HR: 1.13 (95% CI 0.80, 1.60). Similar differences were seen when the analysis was based on prior capecitabine treatment received/not received: HR for eribulin vs. TPC in patients with prior capecitabine was 0.771 (0.612, 0.973), and in patients without prior capecitabine 0.943 (0.617, 1.443).

The updated OS analysis of the capecitabine pre-treated subgroup showed results consistent with the original analysis. The positive effect on OS was seen both in capecitabine-naïve and in capecitabine pre-treated patient groups. The analysis of updated OS showed a survival benefit for the eribulin group compared to TPC both in capecitabine pre-treated patients with a HR of 0.787 (95% CI 0.645, 0.961), and for the capecitabine-naïve patients with a corresponding HR of 0.865 (95% CI 0.606, 1.233). Investigator assessment-based analysis of PFS (based on original data cut-off), also showed a positive effect in the capecitabine pre-treated group with a HR of 0.68 (0.56, 0.83). For the capecitabine-naïve group the corresponding HR was 1.03 (0.73, 1.45).

Table 13: Original and Updated analyses of Overall Survival in relation to pre-study capecitabine therapy received and not received (ITT Population)

Capecitabine status		**Capecitabine pre-treated**				**Capecitabine naïve**			
Analysis and cut-off date		**Original analysis** 12 May 2009		**Updated analysis** 03 March 2010		**Original analysis** 12 May 2009		**Updated analysis** 03 March 2010	
Treatment group		**Eribulin** N = 370	**TPC** N =189	**Eribulin** N = 370	**TPC** N =189	**Eribulin** N = 138	**TPC** N= 65	**Eribulin** N = 138	**TPC** N= 65
Number of patients who died, n (event rate, %)		204 (55.1)	115 (60.8)	291 (78.6)	154 (81.5)	70 (50.7)	33 (50.8)	95 (68.8)	49 (75.4)
Overall Survival	Median, days (95% CI)	394 (355, 434)	306 (235, 348)	395 (355, 421)	308 (235, 356)	408 (338, 559)	365 (304, NE)	454 (346, 556)	346 (304, 535)
	Stratified log-rank test, p-value	0.028		0.018		0.787		0.421	
1-year survival rate, proportion (95% CI)		0.54 (0.49, 0.60)	0.42 (0.35, 0.50)	0.54 (0.49, 0.59)	0.42 (0.35, 0.49)	0.53 (0.44, 0.63)	0.47 (0.34, 0.61)	0.55 (0.47, 0.64)	0.46 (0.34, 0.58)
2- year survival rate, proportion (95% CI)		0.22 (0.14, 0.23)	0.25 (0.15, 0.34)	0.20 (0.16, 0.25)	0.19 (0.13, 0.25)	0.24 (0.10, 0.37)	NE (NE, NE)	0.27 (0.18, 0.35)	0.21 (0.10, 0.32)
Hazard ratio: eribulin/TPC[a] (95% CI)		0.771 (0.612, 0.973)		0.787 (0.645, 0.961)		0.943 (0.617, 1.443)		0.865 (0.606, 1.233)	

CI = Confidence interval, HER/*neu* = human epidermal growth factor receptor 2, ITT = intent-to-treat, N = number of randomised patients in each treatment group, NE = not estimable due to insufficient events, OS = overall survival, TPC = treatment of physician's choice**.**

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

The original PFS analysis according to the Investigator assessment showed a HR of 1.0 for eribulin vs. TPC in the capecitabine-naïve group. In capecitabine pre-treated patients the HR was 0.68 (0.56, 0.83). The results of the direct comparison of capecitabine and eribulin in the randomised phase III Study 301 is expected to further elucidate the comparative efficacy of these two agents.

Summary of main study

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

Table 14: Summary of Efficacy for the pivotal Study 305 – the EMBRACE trial

Title: The 'EMBRACE' Trial: Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389. A Phase 3 Open Label, Randomised Parallel Two-Arm Multi-Center Study of E7389 versus 'Treatment of Physician's Choice' in Patients with Locally Recurrent or Metastatic Breast Cancer, Previously Treated with at Least Two and a Maximum of Five Prior Chemotherapy Regimens, Including an Anthracycline and a Taxane.			
Study identifier	E7389-G000-305		
Design	Phase 3 Open Label, Randomised Parallel Two-Arm Multi-Center Study conducted in 19 countries: Eribulin vs. TPC		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	16.11.2006 (FPFV) – 12.05.2009 (data cut-off) not applicable not applicable	
Hypothesis	Superiority		
Treatments groups	Eribulin 1.23 mg/m^2 (equivalent to 1.4 mg/m^2 eribulin mesylate)	Administered as an IV bolus at 1.23 mg/m^2, administered intravenously over two to five minutes, on Days 1 and 8 of a 21-day cycle. number randomised: 508	
	TPC	Patients treated with either single agent chemotherapy, hormonal or biological therapy, which was available in the investigational center for the treatment of cancer, or, if no such treatment was available, received best supportive care. The use of other investigational drugs, or products not registered for the treatment of cancer was not allowed. number randomised: 254	
Endpoints and definitions	Primary endpoint	OS	OS was defined as the time from the date of randomisation until death from any cause.
	Secondary endpoint	PFS	PFS was defined as the time from the date of randomisation until PD or death from any cause in the absence of disease progression
	Secondary endpoint	Objective tumour response rate (ORR)	ORR was defined as the number of patients with a confirmed CR or confirmed PR divided by the number of patients in the analysis population. The response rate was based on the Independent review of disease assessments.
Database lock	Cut-off date: 12 May 2009		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability and Effect estimate per comparison	Treatment group	Eribulin	TPC
	Number of subject	508	254
	OS No of patients with death (%)	274 (53.9)	148 (58.3)
	Median survival in days (95% CI)	399 (360 - 434)	324 (282 - 380)
	p-value (stratified log-rank)[a]	0.041	

	Hazard Ratio (95% CI) using stratified Cox proportional hazards	0.809 (0.660 - 0.991)	
	[a]: Stratified by geographic region, HER2/*neu* status, and prior capecitabine therapy.		
	PFS - independent review No of patients with PFS events (%)	357 (70.3)	164 (64.6)
	Median progression free survival in days (95% CI)	113 (101 - 118)	68 (63 - 103)
	p-value	0.137	
	Hazard Ratio (95% CI) using stratified Cox proportional hazards	0.865 (0.714 - 1.048)	
	PFS - investigator review No of patients with PFS events (%)	429 (84.4)	206 (81.1)
	Median progression free survival in days (95% CI)	110 (100 - 114)	66 (60 - 79)
	p-value	0.002	
	Hazard Ratio (95% CI) using stratified Cox proportional hazards	0.757 (0.638 - 0.900)	
	ORR – independent review* No of patients with CR + PR (%)	57 (12.2)	10 (4.7)
	95% CI (Exact Pearson-Clopper 2-sided CI)	(9.4 – 15.5)	(2.3 – 8.4)
	p-value (Fisher's exact test)	0.002	
	** Note: the ORR result specified in Section 5.1 of the SmPC is based on randomised patients and not just the response evaluable population*		
	Updated Overall Survival Analysis in the ITT Population at 77% of Events		
	OS No of patients with death (%)	386 (76.0)	203 (79.9)
	Median survival in days (95% CI)	403 (367 - 438)	321 (281 - 365)
	Nominal p-value (stratified log-rank)[a]	0.014	
	Hazard Ratio (95% CI) using stratified Cox proportional hazards	0.805 (0.677 - 0.958)	
	[a]: Stratified by geographic region, HER2/*neu* status, and prior capecitabine therapy.		

Analysis performed across trials (pooled analyses and meta-analysis)

No OS analyses performed across trials were submitted.

Clinical studies in special populations

The efficacy and safety of eribulin in renal dysfunction was investigated in a newly reported study conducted by the National Cancer Institute (NCI) in 21 patients with advanced urothelial cancer (Synold et al 2010), included in the D120 responses. Of 20 evaluable patients, response rate was 20%,1 CR and 3 PR, (95% CI: 7%, 42%). Of 10 patients with SD, 3 patients had unconfirmed PR on 6 week scans but PD at 12 weeks. At median follow-up of 15.8 months, median progression free survival was 4.1 months (19 patients progressed); median survival was 9.7 months.

Efficacy results of PK Study 108 in hepatic impairment have not been reported.

Sub-group analysis of Study 305 (original data cut-off) showed that the HRs for OS according to hepatic and renal function favoured eribulin for all subgroups for which there were sufficient data to allow a comparison. None of the HRs were statistically significant, except the one for the small group with CTC grade 2 baseline AST (also in favour of eribulin), which may be a chance finding.
HRs for OS according to age, race and geographic region favoured eribulin in most subgroups (not statistically significant for any subgroup).

Supportive studies

There were 2 supportive studies (Study 201 and study 211) submitted with the application.
Study 201
Study 201 was an open-label, single-arm, multicenter, proof of concept, Phase II study investigating the efficacy and safety of eribulin in patients with LRBC or MBC previously treated with chemotherapy including an anthracycline and a taxane. Eribulin was initially given at a dose of 1.23 mg/m^2 as a five minute IV bolus on Days 1, 8, and 15 of a 28-day cycle (n=71). Because of the high number of dose delays, reductions, or omissions due to neutropenia on Day 15, the protocol was amended and a second cohort of patients (n=33) was added to explore an alternative regimen administering eribulin on Days 1 and 8 of a 21-day cycle, at the same dose of 1.23 mg/m^2 IV over five minutes.

A total of 104 patients were enrolled in Study 201; 103 patients received treatment, and 87 patients were included in the PP population. Patients were heavily pre-treated, having received a median of 4 prior chemotherapy regimens (range 1 to 11). Patients in the 28-day cohort received a median of 2.5 cycles of eribulin therapy, compared with a median of 4 cycles in the 21-day cohort. ORR was the primary endpoint. Secondary objectives included among others Quality of Life and tumour pharmacogenetics in relation to response.

Study 211
Study 211 was a Phase II, open-label, single-arm study that investigated the efficacy and safety of eribulin in patients with LRBC or MBC previously treated with an anthracycline, a taxane, and capecitabine therapy. Eligible patients for the primary efficacy analysis had to have histologically or cytologically confirmed LRBC or MBC, two to five prior cytotoxic chemotherapy regimens, of which at least one had to be given for advanced disease, progression on or within six months of the last prior chemotherapy regimen, and measurable disease as assessed by Independent radiological review. All patients were to receive eribulin (1.23 mg/m^2) administered as a 2-5 minute IV bolus on Days 1 and 8 of a 21-day cycle.

A total of 299 patients were enrolled and 291 were treated; 269 were evaluable and met the key enrolment criteria based on an independent eligibility review committee (Eligible Population). Patients

were extensively pre-treated, with a median of 4 prior chemotherapy regimens (range 1 to 6). The median number of cycles of eribulin therapy received per patient was 4 (range 1 to 27).

The primary endpoint was the ORR as determined by Independent radiographic review. The primary analysis was based on the Eligible Population. Secondary objective was to evaluate PK/PD relationships in a population PK study.

Results

The phase II Studies 201 and 211 were performed in patients with LRBC or MBC previously treated with chemotherapy including an anthracycline and a taxane (and capecitabine in Study 211). Efficacy results are shown in table 15:

Table 15. Efficacy in Supportive Phase 2 Studies

Population	Analysis/parameter		Study 201			Study 211 (q21 day)
			Both cohorts	q28 day cohort	q21 day cohort	
ITT population	n		103	70	33	291
	OS	median (days)	335	259	-	313
		6 month rate (%)	72	70	76	74
	PFS	median (days)	85	84	86	79
		6 month rate (%)	30	28	36	16
	ORR		14	13	15	9
PP /"Eligible" population*	n		87	59	28	269
	OS	median (days)	275	239	-	315
		6 month rate (%)	68	66	71	72
	PFS	median (days)	79	57	86	79
		6 month rate (%)	26	23	34	16
	ORR (%)		11	10	14	9

* In Study 211 the Eligible population was defined as those evaluable and met the key enrolment criteria according to an independent eligibility review committee. ITT = intention to treat, n = numbers, ORR = objective response rate according to independent review, OS= overall survival, PFS = progression-free survival, PP = per protocol, q= interval.

2.5.3. Discussion on clinical efficacy

The 762 patients in the pivotal Study 305 were women with late stage breast cancer, having received at least 2 prior regimens for advanced disease. They had already received anthracyclines and taxanes as per protocol, and 73% had also received capecitabine (a stratification factor at randomisation). The high proportion of metastasis to the liver (around 60%) and lung (near 40%) indicates that the patient population as a group is in a very advanced stage of disease.

The study met its primary endpoint with an overall survival result that was statistically significantly better in the eribulin group compared to TPC at 55% of events. The median survival of the Halaven group (median: 399 days/13.1 months) compared with the TPC group (median: 324 days/10.6 months) improved by 75 days/2.5 months (HR 0.809, 95% CI: 0.660, 0.991, p=0.041).

The baseline data are overall well balanced, although with small differences (3-4% of patients) in favour of eribulin with regard to the number of patients with liver and lymph node metastasis, and very slight differences (1-3%) regarding number of organs involved, triple-negative tumours (with regard to ER, PgR and HER2 status), and performance status 0. Cancer stage is also in favour of the eribulin group, with 7% (41.8% – 35%) more patients in stage II and 7% (23.2% – 15.9%) less patients in stage IV, compared with the TPC group. In both groups 28% of the patients had stage III disease. Regarding the number of organs involved, 50.6% in the eribulin group had 1-2 involved organs, compared with 46.1% in the TPC group. The prior anti-cancer therapy was overall well balanced between the eribulin and the TPC groups. Small differences were seen in the number of prior

therapies (chemotherapy/hormonal), and patients in the eribulin group tended to have a fewer number of prior therapies, e.g. in the eribulin group 52% of patients had received 4-6 prior cytostatic treatments compared with approximately 55% in the TPC group. The corresponding figures for hormonal therapy were 8 % and 10%, respectively.

However, since using a single pivotal trial for this application, strong support from other outcome measures are required, most importantly PFS. In this Investigator assessed PFS did support the primary endpoint (p=0.002), with HR 0.76 (95% CI 0.64, 0.90). A high concordance was observed between the Independent review and Investigator assessment, and important bias in the adjudication by the investigators can be excluded.
This result was confirmed with an updated overall survival analysis carried out at 77% of events with the median survival of the eribulin group (median: 403 days/13.2 months) compared with the TPC group (median: 321 days/10.5 months) improved by 82 days/2.7 months (HR 0.805, 95% CI: 0.677, 0.958, nominal p=0.014).

In response evaluable patients who received eribulin, the objective response rate by the RECIST criteria was 12.2% (95% CI: 9.4%, 15.5%) by independent review and 13.2% (95% CI: 10.3%, 16.7%) by investigator review. The median response duration in this population by independent review was 128 days (95% CI: 116, 152 days) (4.2 months).

The positive effect on OS and PFS was seen in both taxane-refractory and non-refractory groups of patients. In the OS update, the HR for eribulin versus TPC was 0.90 (95% CI 0.71, 1.14) in favour of eribulin for taxane-refractory patients and 0.73 (95% CI 0.56, 0.96) for patients not taxane-refractory. In the Investigator assessment-based analysis of PFS (based on original data cut-off), the HR was 0.77 (95% CI 0.61, 0.97) for taxane-refractory patients and 0.76 (95% CI 0.58, 0.99) for patients not taxane-refractory.

The positive effect on OS was seen both in capecitabine-naïve and in capecitabine pre-treated patient groups. The analysis of updated OS showed a survival benefit for the eribulin group compared to TPC both in capecitabine pre-treated patients with a HR of 0.787 (95% CI 0.645, 0.961), and for the capecitabine-naïve patients with a corresponding HR of 0.865 (95% CI 0.606, 1.233). Investigator assessment-based analysis of PFS (based on original data cut-off), also showed a positive effect in the capecitabine pre-treated group with a HR of 0.68 (0.56, 0.83). For the capecitabine-naïve group the corresponding HR was 1.03 (0.73, 1.45).

The single-arm studies 201 and 211 both showed activity of eribulin in heavily pre-treated breast cancer patients, i.e. populations similar to that of the pivotal Study 305. The results are poorer than in Study 305, particularly in Study 211 which required prior treatment with capecitabine, unlike the other two studies.

A direct comparison of capecitabine and eribulin as 3rd line treatment in mBC would be of interest. Currently, the ongoing randomised Phase 3 study 301 investigates the efficacy of eribulin compared to capecitabine in the 2nd line setting.

2.5.4. Conclusions on the clinical efficacy

A clinically relevant and statistically significant difference in overall survival has been demonstrated for eribulin compared with the active comparator arm with a difference in median OS 77 days (2.5 months), and difference in 1-year OS rate 10%, p= 0.041 in the original OS analysis based on 55% event rate. This is further supported by an updated OS analysis with 77% event rate which showed consistent results and a lower p-value (0.014).

2.6. Clinical safety

The safety of eribulin has been evaluated in 12 completed clinical studies in different indications, listed in Table 3. The main eribulin safety populations considered included the population of Study 305 (n=503), the Breast Cancer Population (BCP, n= 827) and the All Eribulin Treated Population (AETP, n=1222). The BCP included patients in the 3 efficacy breast cancer studies 305, 201 and 211 who received the target dose applied for. The AETP included 11 of the 12 completed safety studies sponsored by the applicant (one Japanese phase-I study on 15 patients was not included because a translation of results was not available at the time of analysis of the pooled population). The populations are thus to a high degree overlapping, where Study 305 constitutes 61% of the BCP and 41% of the AETP, and the BCP makes up 68% of the AETP. In total, 74% of the patients in the AETP were breast cancer patients.

Patient exposure

The baseline demographic data and disease characteristics of patients in the AETP and the BCP are shown in the following table 16.

Table 16: Summary of demographics and baseline data (safety population)

Parameter	All Eribulin Treated (N=1222) n (%)	Phase 2/3 Breast Cancer Subjects on Target Dose (N=827) n (%)
Age (years)		
Mean (SD)	57.5 (11.48)	55.0 (10.56)
Median	58.0	55.0
Min - Max	26, 91	26, 85
Age Distribution		
≤40 Years	90 (7.4)	76 (9.2)
>40-55 Years	435 (35.6)	339 (41.0)
>55-65 Years	387 (31.7)	274 (33.1)
>65 – 75 Years	244 (20.0)	121 (14.6)
>75 Years	66 (5.4)	17 (2.1)
Weight (kg)		
Mean (SD)	70.9 (15.38)	68.7 (13.55)
Median	69.5	67.0
Min - Max	38, 175	41, 139
Race		
Black	66 (5.4)	37 (4.5)
White	1009 (82.6)	686 (83.0)
Asian/Pacific Islander	21 (1.7)	11 (1.3)
Other	57 (4.7)	27 (3.3)
Missing[a]	69 (5.6)	66 (8.0)
Geographical Region		
North America/Western Europe/Australia	1035 (84.7)	646 (78.1)
Eastern Europe/Russia/Turkey	134 (11.0)	128 (15.5)
Latin America/South Africa	53 (4.3)	53 (6.4)
Total Number of Prior Chemotherapy Regimens [b,c]		
n	999	826
Mean (SD)	3.6 (1.30)	3.7 (1.07)
Median	4.0	4.0
Min, Max	1, 11	1, 10
0	0	0
1	47 (3.8)	4 (0.5)
2	140 (11.5)	99 (12.0)
3	296 (24.2)	265 (32.0)
4	303 (24.8)	283 (34.2)

Parameter	All Eribulin Treated (N=1222) n (%)	Phase 2/3 Breast Cancer Subjects on Target Dose (N=827) n (%)
5	163 (13.3)	148 (17.9)
≥6	50 (4.1)	27 (3.3)
Missing	1 (0.1)	1 (0.1)
Not reviewed[b]	222 (18.2)	0
Number of Subjects Refractory to[d]		
Anthracycline	256 (20.9)	223 (27.0)
Capecitabine	590 (48.3)	539 (65.2)
Gemcitabine	250 (20.5)	179 (21.6)
Taxane	564 (46.2)	443 (53.6)
Vinorelbine	288 (23.6)	252 (30.5)
Number of Subjects Who Previously Received		
Anthracycline	917 (75.0)	821 (99.3)
Avastin	88 (7.2)	76 (9.2)
Capecitabine	766 (62.7)	681 (82.3)
Gemcitabine	358 (29.3)	240 (29.0)
Herceptin	161 (13.2)	138 (16.7)
Herceptin in Her2+ Subjects	108 (84.4)	100 (84.0)
Ixabepilone	10 (0.8)	8 (1.0)
Lapatinib	29 (2.4)	25 (3.0)
Platinum Agent	382 (31.3)	173 (20.9)
Taxane	1074 (87.9)	822 (99.4)
Vinorelbine	387 (31.7)	328 (39.7)
Tumour Type		
Breast Cancer	903 (73.9)	827 (100.0)
NSCLC	112 (9.2)	0
Prostate Cancer	112 (9.2)	0
Other	69 (5.6)	0
Not Reported[e]	26 (2.1)	0

Percentages are based on the number of safety subjects in each integrated analysis set.

[a] Race was not collected in France for study E7389-G000-211.

[b] A centralised categorisation of chemotherapy type and regimen count was not applied for study E7389-G000-204, E7389-A001-101, E7389-A001-102, E7389-E044-103, E7389-E044-108, E7389-E044-109, E7389-E044-110. The information from these 7 studies is not included in this summary item.

[c] Number of prior chemotherapy by regimens was based on Eisai's review.

[d] Refractory is defined as progression during that treatment or within 2 months of the last dose of that chemotherapy regimen.

[e] Tumour type was not reported in study E7389-E044-110.

The duration of eribulin exposure and relative dose intensity in the three safety populations considered (AETP, BCP and Study 305) is shown in Table 17.

Table 17. Exposure and Dose Intensity (Study 305 and Pooled Safety Populations)

Safety population Analysis	All Eribulin Treated Population N=1222	Phase 2/3 breast cancer subjects at eribulin target dose N=827	Study 305	
			Eribulin arm N= 503	Chemotherapy treated in TPC arm N= 238
Number of cycles [a]				
Median	4	5	6	4
Min, Max	1, 47	1, 39	1, 23	1, 31
≥ 6 cycles (% of pts)	38	45	49	33
Duration of exposure (weeks)				
Mean (SD)	17.0 (14.3)	18.3 (13.2)	19.6 (13.2)	14.1 (13.6)
Median	12.3	15.1	16.9	9.1
Min, Max	3, 153	3, 125	3, 71	0, 92
Dose intensity (mg/m2/week)				
Mean (SD)	0.79 (0.18)	0.80 (0.16)	0.78 (0.166)	-
Median	0.85	0.86	0.85 (0.2, 1.0)	-

Min, Max	0.1, 1.3	0.2, 1.0	0.2, 1.0	-
Relative dose intensity				
Mean (SD)	0.85 (0.17)	0.85 (0.17)	0.84 (0.178)	-
Median	0.92	0.92	0.91	-
Min, Max	0.3, 1.3	0.3, 1.1	0.3, 1.1	-

Duration of Exposure (weeks) = (Date of day 1 of last cycle - first dose date + Length of cycle)/7.
Dose Intensity = Total dose received during the study/ (duration of exposure/7).
Relative Dose Intensity = Dose Intensity (mg/m2/week) / Planned dose intensity.
a: TCP cycles included 3 and 4-week cycles.

Adverse events

Table 19 provides an overview of Treatment Emergent Adverse Events (TEAEs) in the pooled safety populations.

Table 18: Overall Incidence of Adverse Events (AEs, AETP and BCP)

Category	All Eribulin Treated (N=1222) n (%)	Phase 2/3 Breast Cancer Subjects on Target Dose (N=827) n (%)
AEs	1210 (99.0)	820 (99.2)
AEs Reported as Treatment-Related	1148 (93.9)	790 (95.5)
Serious AEs	358 (29.3)	224 (27.1)
Serious AEs Reported as Treatment-Related	152 (12.4)	101 (12.2)
Death	68 (5.6)	39 (4.7)
Death Reported as Treatment-Related	10 (0.8)	6 (0.7)
AE Leading to Treatment Discontinuation	168 (13.7)	107 (12.9)
AE Leading to Treatment Discontinuation Reported as Treatment-related	97 (7.9)	66 (8.0)
AE Leading to Treatment Interruption	51 (4.2)	26 (3.1)
AE Leading to Treatment Delay	322 (26.4)	296 (35.8)
AE Leading to Treatment Reduction	159 (13.0)	125 (15.1)

Percentages are based on the number of safety subjects in each integrated analysis set.
AE= Adverse Event
For each row category, a subject with two or more AEs in that category is counted only once.

In Study 305, the most frequently reported (reported for 20% or more of patients) AEs among patients treated with eribulin were asthenia/fatigue (53.7%), neutropenia (51.7%), alopecia (44.5%), peripheral neuropathy (34.6%), nausea (34.6%), constipation (24.7%), leucopenia (23.1%), arthalgia/myalgia (21.7%), weight decreased (21.3%), and pyrexia (20.9%).

The majority of the common AEs (regardless of relationship) were CTCAE Grade 1 or 2. Neutropenia, leucopenia, peripheral neuropathy, and asthenia/fatigue were the most common AEs reported at CTCAE Grades 3 and 4. Neutropenia was the most common AE reported at CTCAE Grade 4 in the eribulin group (24.1%).

In the pooled analysis, the most frequently reported AEs were asthenia/fatigue, neutropenia, alopecia, nausea, and peripheral neuropathy. In the BCP, neutropenia (54.5%), asthenia/fatigue (52.8%), alopecia (49.7%), nausea (35.1%), peripheral neuropathy (32.0%), leucopenia (22.1%), and anaemia (20.3%) were the most frequently reported (reported for 20% or more of patients) adverse drug reactions.

The AEs in the pooled populations are shown in greater detail in the following Table 20.

Table 19: AEs with at least 10% incidence in either population by SOC and PT (pooled safety populations)

MedDRA Preferred Term	All Eribulin Treated (N=1222) n (%)	Phase 2/3 Breast Cancer Subjects on Target Dose (N=827) n (%)
Blood and lymphatic system disorders	**787 (64.4)**	**534 (64.6)**
Neutropenia	651 (53.3)	457 (55.3)
Anaemia	316 (25.9)	187 (22.6)
Leucopenia	258 (21.1)	186 (22.5)
Gastrointestinal Disorders	**857 (70.1)**	**564 (68.2)**
Nausea	479 (39.2)	329 (39.8)
Constipation	354 (29.0)	229 (27.7)
Diarrhoea	253 (20.7)	165 (20.0)
Vomiting	251 (20.5)	170 (20.6)
General disorders and administration site conditions	**927 (75.9)**	**621 (75.1)**
Asthenia + fatigue[a]	736 (60.2)	495 (59.9)
Fatigue	476 (39.0)	273 (33.0)
Asthenia	305 (25.0)	247 (29.9)
Pyrexia	285 (23.3)	198 (23.9)
Oedema peripheral	164 (13.4)	90 (10.9)
Mucosal inflammation	113 (9.2)	87 (10.5)
Infections and infestations	**518 (42.4)**	**353 (42.7)**
Urinary tract infection	127 (10.4)	89 (10.8)
Investigations	**344 (28.2)**	**241 (29.1)**
Weight decreased	177 (14.5)	137 (16.6)
Metabolism and Nutrition Disorders	**507 (41.5)**	**319 (38.6)**
Decreased appetite	332 (27.2)	206 (24.9)
Musculoskeletal and connective tissue disorders	**664 (54.3)**	**464 (56.1)**
Arthralgia + myalgia [a]	263 (21.5)	192 (23.2)
Back pain	171 (14.0)	126 (15.2)
Arthralgia	165 (13.5)	123 (14.9)
Myalgia	132 (10.8)	98 (11.9)
Pain in extremity	129 (10.6)	97 (11.7)
Bone pain	125 (10.2)	88 (10.6)
Nervous system disorders	**714 (58.4)**	**503 (68.8)**
Peripheral neuropathy based on broad MedDRA SMQ [ab]	497 (40.7)	343 (41.5)
Peripheral neuropathy [c]	404 (33.1)	289 (34.9)
Headache	212 (17.3)	169 (20.4)
Neuropathy peripheral	182 (14.9)	113 (13.7)
Peripheral sensory neuropathy	119 (9.7)	94 (11.4)
Paraesthesia	118 (9.7)	90 (10.9)
Respiratory, thoracic and mediastinal disorders	**542 (44.4)**	**344 (41.6)**
Dyspnoea	229 (18.7)	144 (17.4)
Cough	209 (17.1)	136 (16.4)
Skin and subcutaneous tissue disorders	**662 (54.2)**	**483 (58.4)**
Alopecia	535 (43.8)	417 (50.4)

Adverse Event Coding Dictionary: MedDRA Version 12.1.
Percentages are based on the number of safety subjects in each integrated analysis set.
A subject with two or more adverse events in the same preferred term is counted only once for that preferred term.
Summary is sorted by descending order of frequency in All Eribulin Treated column.
a: Combined MedDRA terms, also reported separately
b: Broad list of peripheral neuropathy terms: The broad Standard MedDRA Query (SMQ) v12.1 of preferred terms for peripheral neuropathy supplemented to include the following additional terms: hyperesthesia, painful response to stimuli, pallanesthesia, and allodynia.
c: Peripheral Neuropathy includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paraesthesia

In study 305, the most common AEs reported by the Investigator as related to eribulin (adverse drug reactions) were neutropenia (50.7%), asthenia/fatigue (45.5%), alopecia (44.1%), peripheral neuropathy (31.6%), nausea (29.8%), and leucopenia (22.7%).The most commonly reported adverse reactions to eribulin in the BCP are shown in Table 20 below. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Actual frequencies are shown where Grade 3 or 4 reactions occurred with a frequency of ≥ 1%.

Table 20: Very common and common ADRs and grade 3 and 4 ADRs with at least 1% frequency in the BCP

System Organ Class	**Adverse Reactions – all Grades**		**Grade 3 and 4 Reactions ≥ 1% Frequency %**
	Very Common (Frequency %)	**Common (Frequency %)**	
Infections and infestations		Urinary tract infection Oral candidiasis Upper respiratory tract infection Nasopharyngitis Rhinitis	
Blood and lymphatic disorders	Neutropenia (54.5%) Leucopenia (22.1%) Anaemia (20.3%)	Febrile neutropenia (4.7%) Thrombocytopenia Lymphopenia	Neutropenia 48.3% Leucopenia 14% Febrile neutropenia 4.6%[a] Anaemia 1.4%
Metabolism and nutrition disorders	Decreased appetite	Hypokalaemia Hypomagnesaemia Dehydration Hyperglycaemia Hypophosphataemia	
Psychiatric disorders		Insomnia Depression	
Nervous system disorders	Peripheral neuropathy [b] (32.0%) Headache	Dysgeusia Dizziness Hypoaesthesia Lethargy Neurotoxicity	Peripheral neuropathy [b] 6.9%
Eye disorders		Lacrimation increased Conjunctivitis	
Ear and Labyrinth Disorders		Vertigo	
Cardiac disorders		Tachycardia	
Vascular disorders		Hot flush	
Respiratory, thoracic and mediastinal disorders		Dyspnoea Cough Oropharyngeal pain Epistaxis Rhinorrhoea	
Gastrointestinal disorders	Nausea (35.1%) Constipation Diarrhoea Vomiting	Abdominal pain Stomatitis Dry mouth Dyspepsia Gastrooesophageal reflux disease Mouth ulceration Abdominal distension	Nausea 1.1%[c]

Hepatobiliary disorders		Alanine aminotransferase increased (3.0%) Aspartate aminotransferase increased	Alanine aminotransferase increased 1.1%[c]
Skin and subcutaneous tissue disorders	Alopecia	Rash Pruritus Nail disorder Night sweats Palmar plantar erythrodysaesthesia Dry skin Erythema Hyperhidrosis	
Musculoskeletal and connective tissue disorders	Arthralgia and Myalgia	Pain in extremity Muscle spasms Musculoskeletal pain and Musculoskeletal chest pain Muscular weakness Bone pain Back pain	
General disorders and administrative conditions	Fatigue/Asthenia (52.8%) Pyrexia	Mucosal Inflammation (9.8%) Peripheral oedema Pain Chills Influenza like illness Chest Pain	Fatigue/Asthenia 8.4% Mucosal Inflammation 1.3%[c]
Investigations		Weight decreased	

[a] Includes 1 grade 5
[b] Includes preferred terms of peripheral neuropathy, peripheral motor neuropathy, polyneuropathy, paraesthesia, peripheral sensory neuropathy, peripheral sensorimotor neuropathy and demyelinating polyneuropathy
[c] No grade 4

In the same population (BCP) the following medically significant adverse reactions were reported as uncommon (≥ 1/1,000 to < 1/100)

Infection and infestations: Pneumonia, Neutropenic sepsis, Oral herpes, Herpes zoster

Ear and labyrinth disorders: Tinnitus

Vascular disorders: Deep vein thrombosis, pulmonary embolism

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease

Hepatobiliary disorders: Hyperbilirubinaemia

Skin and subcutaneous tissue disorder: Angioedema

Renal disorders: Dysuria, Haematuria, Proteinuria, Renal failure

Serious adverse event/deaths/other significant events

Serious adverse events

Serious AEs were reported for 29 and 27% of the subjects in the All Eribulin Treated and Breast Cancer populations, respectively. In both populations, the five most commonly reported serious AEs were febrile neutropenia (47 [3.8%] and 32 [3.9%]), pyrexia (29 [2.4%] and 18 [2.2%]), dyspnoea (24 [2.0%] and 16 [1.9%]), neutropenia (21 [1.7%] and 16 [1.9%]), and pleural effusion (19 [1.6%] and 14 [1.7%].

In the All Eribulin Treated Population, 152 (42.4%) subjects had AEs that were reported as at least possibly related to treatment by the investigator, respectively. In the Breast Cancer population, serious AEs were reported as at least possibly related to treatment by the investigator for 101 (45.1%) subjects, respectively.

In both the All Eribulin Treated and Breast Cancer Populations, serious AEs of febrile neutropenia (43/47 [91.5%] and 29/32 [90.6%]), neutropenia (19/21 [90.5%] and 14/16 [87.5%]), and peripheral neuropathy (5/6 [83.3%] and 5/5 [100%]) were considered probably related to treatment by the investigator for most subjects, with the other serious AEs being considered possibly related to treatment. A large proportion of cases of pyrexia were considered possibly or probably related in both populations (19/29 [65.5%] subjects and 13/18 [72.2%] subjects, respectively). Similarly, pulmonary embolism was considered probably or possibly related in 6/16 [37.5%] and 3/7 [42.9%] cases.

With the exception of one Grade 5 serious AE (a death), all other serious AEs of febrile neutropenia in both populations (46 [3.8%] and 31 [3.8%] respectively), were Grade 3+4. In each population, there were 5/6 [83.3%] and 4/5 [80%] subjects with Grade 3+4 serious TEAEs of peripheral neuropathy, respectively

Deaths

Table 21 provides a listing of all AEs with outcome of death that is not due to disease progression in breast cancer studies 201, 211 and 305. Of the 21 deaths, 7 were considered possibly or probably related to treatment by the investigator.

Table 21: Deaths not due to disease progression in the BCP

Cases	Age (Years)	Preferred Term	Verbatim Term	Duration (Days)	CTC Grade/ Severity	Relation to Study Drug
Study 201: Eribulin Non-Target Dose						
1	50	Respiratory failure	Respiratory Failure	1	5	Not related
2	75	Neutropenic sepsis	Neutropenic sepsis[c]	8	5	Probably related
		Thrombocytopenia	Thrombocytopenia	8	3	Probably related
3	60	Pyrexia	Fever	401	2	Not related
Study 211: Eribulin Target Dose						
4	58	Respiratory failure	Respiratory failure	1	5	Not related
5	67	Respiratory failure	Respiratory tract failure	5	5	Not related
6	56	Death	Unexpected death due to unknown reason	1	5	Possibly related
7	59	Cardiac arrest	Cardiac arrest	1	5	Not related
8	38	Pleural effusion	Pleural effusion both sides	14	5	Not related
9	62	Cerebrovascular accident	Cerebral stroke	6	5	Not related
Study 305: Eribulin Target Dose						
10	56	Febrile neutropenia	Febrile neutropenia	2 / 43	5	Probably related
11	54	Respiratory failure	Respiratory failure	3 / 84	2/ moderate	Not related
12	49	Paraparesis	Lower paraparesis	9 / 185	4/ severe	Not related
13	71	Diabetic ketoacidosis	Diabetic Ketoacidosis	1 / 12	5	Not related
14	52	Lung infection	Pulmonary infection	3 / 64	5	Probably related
15	44	Pulmonary embolism	Pulmonary thromboembolism	7 / 139	5	Not related
16	48	Meningeal disorder	Leptomenengial disease	1 / 18	5	Not related
17	69	Dyspnoea	Dyspnoea	4 / 103	5	Not related
18	55	Bronchopneumonia	Bronchopneumonia	2 / 34	5	Possibly

Cases	Age (Years)	Preferred Term	Verbatim Term	Duration (Days)	CTC Grade/ Severity	Relation to Study Drug
						related
19	60	Dyspnoea	Dyspnoea	1 / 23	5	Possibly related
20	45	Sepsis	Sepsis	2 / 37	5	Not related
21	53	Dyspnoea	Dyspnoea	1 / 20	5	Possibly related

Adverse Event Coding Dictionary: MedDRA Version 12.1.

Day of Onset = AE Start Date - First Dose Date +1.

Narrative contains details of other medical conditions and concomitant medications.

Laboratory findings

The number and percentage of subjects who experienced the most frequently reported abnormal chemistry values at any post-baseline visit are summarised in Table 22. Overall, for both populations, there was a low incidence (≤6.4%) of abnormal chemistry values.

Table 22: Abnormal chemistry values overall for all cycles (safety population)

Laboratory Tests	All Eribulin Treated (N=1222) n (%)	Phase 2/3 Breast Cancer Subjects on Target Dose (N=827) n (%)
Hypophosphataemia	74/1160 (6.4)	49/ 796 (6.2)
Hyperglycemia[a]	29/ 566 (5.1)	13/ 322 (4.0)
Hyponatraemia	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)
Hypokalaemia	43/1218 (3.5)	37/ 826 (4.5)
Alanine Aminotransferase	33/1218 (2.7)	28/ 826 (3.4)
Hypomagnesaemia	26/1093 (2.4)	21/ 788 (2.7)
Hypocalcaemia	22/1211 (1.8)	17/ 827 (2.1)
Hypoalbuminemia	21/1207 (1.7)	10/ 815 (1.2)
Hypercalcaemia	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)
Hyperkalaemia	13/1218 (1.1)	9/ 826 (1.1)
Creatinine increased	11/1217 (0.9)	6/ 827 (0.7)
Hypomagnesaemia	6/1093 (0.5)	6/ 788 (0.8)
Hypoglycaemia	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.

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

Hypophosphataemia was the most frequent abnormal chemistry laboratory value (defined as a change of at least 2 CTCAE grades from grade 0-2 at baseline or a change from grade 3-4 to a higher value) in the pooled populations, occurring in 6% of both populations.

Hyperglycaemia was the second most frequent abnormal chemistry value, occurring in 5% of the patients in the AETP, and 4 % in the BCP.

The number and percentage of subjects who experienced the most frequently reported abnormal haematological values at any post-baseline visit are summarized in Table 23.

Abnormal absolute neutrophil count was the most common haematological abnormality. In the Breast Cancer Population, abnormal Absolute Neutrophil Count (ANC) values were reported for approximately

60% of subjects, although these were reported as AEs of neutropenia of at least Grade 3 or higher for only 48.9% of subjects.

Table 23: Patients with abnormal haematology values overall for all cycles (safety population)

Laboratory Tests	All Eribulin Treated (N=1222) n (%)	Phase 2/3 Breast Cancer Subjects on Target Dose (N=827) n (%)
ANC	665/1217 (54.6)	493/ 825 (59.8)
WBC	428/1220 (35.1)	317/ 827 (38.3)
Haemoglobin	35/1220 (2.9)	19/ 827 (2.3)
Platelet Count	17/1220 (1.4)	12/ 827 (1.5)

Percentages are based on the total number of subjects with non-missing lab measurement in relevant cycle and each integrated analysis set. ANC: absolute neutrophil count, WBC: white blood cells

Safety in special populations

Renal impairment

Eribulin is minimally excreted via the kidney. Sub-group analysis of the pooled safety populations based on baseline creatinine clearance showed trends of higher frequencies of treatment-related AE any grade and grade 3-4, and neutropenia in patients with serum-creatinine clearance levels below normal, but the groups with low values were small, together less than 15% of the populations. In this setting an abnormal creatinine value is likely to be related to a poorer disease status overall, hence these data may not specifically reflect an independent effect of eribulin on renal impairment.

A newly reported NCI sponsored phase I study of renal impairments (Synold et al 2010) in 21 patients with advanced urothelial cancer showed a MTD of 1.23 mg/m^2 eribulin (which is the normal dose applied for) in patients with moderate renal dysfunction (defined as creatinine clearance ≥40-59 mL/m, Cockroft-Gault), and no dose limiting toxicities (DLTs) were seen. In patients with severe renal dysfunction (creatinine clearance 20-40 mL/m, not needing dialysis) 1 of 6 patients at 1.23 mg/m^2 had DLT (grade 3 muscle weakness and grade 3 hypoalbuminemia). The eribulin exposure was increased in patients with creatinine clearance below 30-40 ml/min, which could be caused by reduced biliary transporter expression.

Hepatic impairment

The effect of hepatic impairment on eribulin exposure was studied in Study 108 (n=17). The study showed that hepatic impairment increased the mean dose-normalized eribulin Cmax, and increased exposure to eribulin.

Patients in the AETP and BCP with abnormal serum liver function values (bilirubin, ALT and AST) had more grade ≥ 3 treatment-related AEs and SAEs. Specifically, all types and grades of neutropenia events increased consistently with increasingly pathological laboratory values for all three measurements, and peripheral neuropathy increased with ALT /AST, whereas asthenia/fatigue appeared not to be affected. Patients with ALT or AST > 3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin > 1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia

(The dose of eribulin was reduced according to protocol in cases of grade ≥3 non-haematological toxicity. Toxicity reverted to grade ≤2 before next treatment.)

Gender

The present application only concerns women in the advanced breast cancer population. A minority of men were included in the AETP in non-breast cancer studies. Women had more treatment-related AEs of interest including grade 3-4 events.

Race

The vast majority of patients in the AETP and BCP were white, constituting 83% of patients in both populations. The other races included were Black: 5 and 4% of the AETP and BCP, respectively, Asian/Pacific Islander: 2 and 1 %, and Other: 5 and 3%, respectively.

No meaningful differences were seen in AEs of special interest, including neutropenia, febrile neutropenia, asthenia/fatigue, peripheral neuropathy or alopecia, nor in all TEAEs of any grade, SAEs. The duration of exposure was similar across groups.

Age

In the AETP (n= 1222), 244 patients (20.0%) were >65 to 75 years of age and 66 subjects (5.4%) were >75 years of age. The median duration of exposure and dose intensity was the same for all age groups, as were the frequencies of any treatment-related AEs and SAEs, including neutropenia and peripheral neuropathy. Population pharmacokinetic (PK) analyses showed that eribulin exposure in elderly subjects was similar to that in younger subjects.

Among the 827 of these patients who received the recommended dose of eribulin in the Phase 2/3 breast cancer studies, 121 patients (14.6%) were > 65 - 75 years of age and 17 patients (2.1%) were > 75 years of age. The safety profile of eribulin in elderly patients (> 65 years of age) was similar to that of patients ≤ 65 years of age therefore no dose adjustments was considered necessary for the elderly population. Data in patients > 80 years of age is limited.

Immunological events

There were no anaphylactoid reactions reported. First dose hypersensitivity reactions occurred in only 1% of subjects of the AETP and BCP. The frequency was 1% in both patients who received and ones who did not receive (anti-emetic) therapy with corticosteroids and/or H1 antihistamine on Day 1 Cycle 1. In all cycles, grade 3-4 allergic conditions that occurred on or within 2 days of first dose were reported for 10 (0.8%) and 9 (1.1%) subjects, respectively. Sixteen MedDRA Preferred terms that can be related to allergic reactions, including Hypersensitivity terms, different Rash and Pruritus terms, Angio-oedema, Face oedema, and Flush, among others, affected 98 (8 %) patients of the AETP and 74 (9 %) of the BCP; grade ≥ 3 events constituted 0.3 and 0.2%, respectively.

Safety related to drug-drug interactions and other interactions

No relevant drug-drug interactions have been identified based on PK data so far but the transport protein involved in the biliary excretion of eribulin, which is the main elimination pathway, has not been identified (see discussion on Clinical Safety).

Discontinuation due to adverse events

Treatment discontinuation due to AE occurred in 168 (14%) patients in the AETP; 71 (6%) of these were considered not related, while 97 (8%) were considered possibly/probably related. In the BCP 107 (13%) patients had any AE leading to treatment discontinuation; for 41 (5%) these were not related, 66 (8%) were possibly/probably related (see Table 19-beginning of safety section).

AEs leading to discontinuation of treatment included among others: neutropenia, febrile neutropenia, asthenia/fatigue, peripheral neuropathy and vomiting.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The duration of eribulin exposure and relative dose intensity were very similar between the three partly overlapping safety populations studied (AETP, BCP and Study 305). A high percentage (38-49%) of all three eribulin populations received ≥ 6 cycles of therapy, which suggests both effect and tolerability of the drug. The median duration of exposure was considerably higher in the eribulin arm (17 weeks) compared with the TPC-arm (9 weeks) of Study 305.

In study 305, the toxicity profile of eribulin was more or less as can be expected from a tubulin-active chemotherapeutic agent. The most common AEs in the eribulin arm were asthenia & fatigue (53.7%), neutropenia (51.7%), alopecia (44.5%), nausea (34.6%), peripheral neuropathy (34.6%), constipation (24.7%) and leucopenia (23.1%). No important differences between the eribulin and the TCP arm were observed.

The two pooled safety populations, the All eribulin treated population (AETP, n= 1222) and the Breast cancer population (BCP, n= 827), had very similar frequencies of AEs, although often slightly higher than Study 305. In the AETP and BCP asthenia/fatigue occurred in 60%, neutropenia in 53-55%, nausea in 39-40%, and peripheral neuropathy in around 34 %. The dominating SAE was febrile neutropenia occurring in 4%. Thromboembolic SAEs (pulmonary embolism and deep vein thrombosis) occurred in a frequency of ≤ 2%, which is around what may be expected in this disease and therapy setting (Stein et al, Am J Med, 2006). The pattern of AEs and SAEs is consistent with that of a tubulin-acting cytotoxic agent.

Myelosuppression was primarily manifested as neutropenia which was dose-dependent, reversible and not cumulative; the mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (< 0.5 $x10^9$/l) was 8 days. Neutrophil counts of < 0.5 $x10^9$/l that lasted for more than 7 days occurred in 13% of breast cancer patients treated with eribulin. Febrile neutropenia occurred in < 5% of breast cancer patients treated with eribulin.

Severe neutropenia may be managed by the use of G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines. 18% of breast cancer patients treated in a phase 3 study with eribulin received G-CSF.

Patients with ALT or AST >3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin >1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Treatment with eribulin should only be initiated in patients with ANC values ≥ 1.5 x 10^9/L and platelets > 100 x 10^9/l. Also complete blood counts should be performed on all patients prior to each dose of

eribulin. Dose reductions and dose delays related to haematological and non-haematological adverse reactions have been proposed by the applicant and are considered acceptable (see section 4.2)

In the 827 breast cancer patients 35% of patients experienced peripheral neuropathy. The median time to Grade 2 peripheral neuropathy was 85 days (post 4 cycles). Development of grade 3 or 4 peripheral neuropathy occurred in 7% of eribulin treated breast cancer patients. Patients with pre-existing neuropathy were as likely to develop new or worsening symptoms as those who entered the study without the condition. In patients with pre-existing Grade 1 or 2 peripheral neuropathy, the frequency of treatment-emergent Grade 3 peripheral neuropathy was 10%. Analyses of treatment-related AEs in relation to cumulative doses and exposure of eribulin suggest that peripheral neuropathy is a cumulative toxicity, in line with other tubulin-targeting drugs. In most cases the neuropathy resolved, in the sense of returning to baseline or lower, during or after the treatment period. An accurate estimation of the time to (complete) resolution is however not possible, due to a large number of censorings. The most feared peripheral *motor* neuropathy was experienced by only 5% of the patients. Adequate warning has been included in section 4.4 of the SmPC.

The applicant will provide data on frequency of resolution and time-to-resolution of peripheral neuropathy from study 209 as reflected in the RMP (see section 2.7).

In the BCP

The incidence of treatment-related nausea and vomiting (36% and 14%, respectively, in the BCP) would motivate antiemetic premedication with one dose of corticosteroids, according to international recommendations (Kris et al). Forty-six percent of patients received anti-emetic prophylaxis during cycle1, half of which included the steroid dexamethasone. While corticosteroid anti-emetic prophylaxis may not be required for all patients, it should be considered and this is mentioned in section 4.2 of the SmPC.

Of the 17 AEs with an outcome of death unrelated to disease progression that occurred in the BCP (n= 827) during study or within 30 days of last dose/visit, only 6 were reported as possibly or probably treatment-related, 3 of which were infections, which can be expected of immunosuppressive agents like eribulin. Thus, in both the pivotal study and the BCP safety population treatment-related deaths occurred in a frequency of ≤ 1 %.

The pattern of abnormal haematological values appeared mainly due to the direct bone marrow suppression and primarily affected neutrophils, in a manner typical of cytotoxic compounds.

Eribulin is minimally excreted via the kidney. Sub-group analysis of the pooled safety populations showed trends of increased toxicity in patients with serum-creatinine clearance levels below normal, but the groups were small. Moreover, in this setting an abnormal creatinine value is likely to be related to a poorer disease status overall, thus these data may not reflect an independent effect of eribulin on renal impairment specifically.

In a newly reported NCI sponsored phase I study of renal impairment s (Synold et al 2010) in 21 patients with advanced urothelial cancer, 1of 6 patients with severe renal dysfunction (creatinine clearance 20-40 mL/m, not needing dialysis) had DLT (grade 3 muscle weakness and grade 3 hypoalbuminemia) at the recommended dose of 1.23 mg/m^2. The eribulin exposure was increased in patients with creatinine clearance below 30-40 ml/min, which could be caused by reduced biliary transporter expression (see Clinical Pharmacokinetics). In order to discuss potential treatment recommendations for patients with different degrees of renal impairment, the applicant will submit as part of the risk management plan, the available rich data (the NCI study and the pooled study data) using renal function as a continuous variable. Patients with severely impaired renal function (creatinine

clearance <40 ml/min) may need a reduction of the dose although the optimal dose for this patient groups remains to be established. In patients with mild to moderate renal impairment, no specific dose adjustments are recommended.

Patients with ALT or AST >3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin >1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia.

In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmia, medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmic, and electrolyte abnormalities. Hypokalaemia or hypomagnesaemia should be corrected prior to initiating Halaven and these electrolytes should be monitored periodically during therapy. Eribulin should be avoided in patients with congenital long QT syndrome.

As the studies that included men concern different populations than the female advanced breast cancer population (which constitutes the majority of women exposed to eribulin), the differences in AEs between men and women may be confounded by differences unrelated to gender.

No specific dose adjustments were recommended based on age of the patient and none appears necessary.

The frequency of hypersensitivity reactions does not justify pre-medication.

In one case of overdose the patient inadvertently receiving 8.6 mg of eribulin mesylate (approximately 4 times the planned dose) subsequently developed a hypersensitivity reaction (Grade 3) on Day 3 and neutropenia (Grade 3) on Day 7. Both adverse reactions resolved with supportive care.

There is no known antidote for eribulin overdose. In the event of an overdose, the patient should be closely monitored and the presenting clinical manifestations adequately treated.

No relevant drug-drug interactions have been identified based on PK data so far but the transport protein involved in the biliary excretion of eribulin, which is the main elimination pathway, has not been identified. A trend for subjects taking concomitant CYP3A4 inhibitors to have a higher percentage of serious AEs, deaths and AEs leading to treatment discontinuations was observed during the clinical studies. A possible explanation could be that these patients had concomitant infections (the most commonly used CYP3A4 inhibitors were fluconazole and clarithromycin). Another explanation is increased systemic or local exposure of eribulin through P-gp inhibition by these drugs. In Study 109 co-administration of eribulin with ketoconazole, a potent CYP3A4 inhibitor, was studied and ketoconazole had no effect on eribulin exposure. Ketoconazole is stated to be a mild to moderate P-gp inhibitor but clear evidence for this is presently lacking, hence extrapolation of results to known potent P-gp inhibitors should be made with caution. Eribulin does not inhibit the CYP enzymes CYP1A2, 2C9, 2C19 and 2D6 at relevant clinical concentrations.

There is no experience of using eribulin in combination with anti-HER2 therapy in clinical trials.

The AE most often causing discontinuation of treatment was peripheral neuropathy at around 4% in the BCP and AETP. Asthenia/fatigue caused discontinuation in approximately 1%, and neutropenia/febrile neutropenia in < 1% of patients. This pattern is consistent with a tubulin acting cytotoxic agent.
The risk of asthenia and fatigue may lead to a minor or moderate influence on the ability to drive or use machines. This is reflected in section 4.7 of the SmPC

2.6.2. Conclusions on the clinical safety

Overall, the safety and tolerability of eribulin in latter lines of therapy for advanced disease may be considered sufficiently established to enable a B/R assessment.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan identifying relevant important identified/potential risks and important missing information.

Table 24: Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Myelosuppression and associated Infections	Routine pharmacovigilance Clinical trial design to protect safety of the subjects (i.e. monitoring, exclusion criteria, AE reporting)	Warning in section 4,4 of SmPC that dose dependent myelosuppression may occur and that monitoring of blood counts should be performed on all patients prior to each dose of eribulin. Also that patients with hepatic impairment may experience a higher incidence of grade 4 neutropenia or febrile neutropenia. Information on incidence of myelosuppression and associated infection also in section 4,8 of SmPC
Peripheral Neuropathy	Routine pharmacovigilance Safety analyses of ongoing phase 2 study (E7389-G000-209) to evaluate differences in development neurotoxicity during treatment with Eribulin The frequency of resolution and time to-resolution of peripheral neuropathy will be reported based on the results of the study E7389-G000-209 Clinical trial design to protect safety of the subjects (i.e. monitoring, exclusion criteria, AE reporting)	Warning in section 4,4 of SmPC to monitor patients for signs of peripheral and sensory neuropathy. Information on incidence and course of neuropathy also in section 4,8 of SmPC
Nausea/Vomiting	Routine pharmacovigilance	Information on use of anti-emetics as required given in section 4,2 of SmPC. Information on incidence of nausea and vomiting in section 4,8 of SmPC
Depression & Insomnia	Routine pharmacovigilance	Information on incidence and course of insomnia and depression in section 4.8 of SmPC
Tachycardia	Routine pharmacovigilance	Information on incidence and course of tachycardia in section 4.8 of SmPC
Adverse pregnancy outcome	Routine pharmacovigilance	Warning to avoid eribulin in pregnancy unless benefit outweighs the risks in section 4,6 of SmPC
Male infertility	Routine pharmacovigilance	Information on testicular toxicity and advice to male patients to conserve sperm prior to treatment given in section 4,6 of SmPC
Important missing information		
Patients with	Routine pharmacovigilance	- The use of eribulin in patients with severe

Hepatic Impairment	Additional activities: - Separate graphs on the relationship between AUC and S-bilirubin, PT, and S-albumin based on data from the hepatic impairment study (E7389-E044-108) will be presented within 6 months of licensing - Support for extrapolation of the results in patients with metastases to patients with cirrhosis based on available scientific literature will be provided within 6 months of licensing.	hepatic impairment (Child-Pugh C) has not been studied. Reduction of the starting dose in patients with mild hepatic impairment (Child-Pugh A) and moderate hepatic impairment (Child-Pugh B) is recommended. - Any adverse events reported in patients with hepatic impairment will be closely monitored in the post-marketing environment. Dose recommendation may be proposed based on one or more of these variables. Consideration will be given to an appropriate initial dose for hepatic impairment due to cirrhosis taking the possible uncertainty into account.
Patient with Renal impairment:	Routine pharmacovigilance Additional activities: Available rich data from the NCI study and the pooled study data in separate graphs using renal function as continuous variable will be presented and discussed within 6 months of licensing .	- Based on the population pharmacokinetic analysis, renal impairment is not expected to significantly influence eribulin exposure. - No specific dose adjustments are recommended for patients with renal impairment. - Any adverse events reported in patients with renal impairment will be closely monitored in the post-marketing environment. - Based on the information available, suitable treatment recommendations for patients with different degrees of renal impairment will be considered for inclusion in the SmPC
Patients with Cardiovascular impairment:	Routine pharmacovigilance	- Eribulin has not been studied in population with significant cardiovascular impairment and patients with history of congestive heart failure > NYHA Grade II, unstable angina or myocardial infarction within the past six months, or serious cardiac arrhythmia were excluded from the studies. - No specific dose adjustments are recommended for patients with cardiac impairment. - Any adverse events reported in patients with cardiac impairment will be closely monitored in the post-marketing environment
Elderly	Routine pharmacovigilance	- No dose adjustments are recommended based on the age for elderly patients. - Any adverse events reported in elderly patients will be closely monitored in the post-marketing environment
Male patients	Routine pharmacovigilance	- Eribulin has not been studied in male patients with breast cancer but male patients have participated in Eribulin studies for prostate cancer and lung cancer.
Pregnant women	Routine pharmacovigilance	Any reports of pregnancy on the post-marketing environment will be closely followed up and reported in PSURs
Drug-Drug interactions	Additional activities: A list of potent inhibitors of hepatic uptake and efflux transporter inhibitors which could be involved in eribulin biliary excretion will be proposed within 6 months of licensing. - Extensive *in vitro* studies aimed at identifying the transporter involved in the marked biliary excretion of eribulin will be	This list will be considered for inclusion in the SmPC. In addition, treatment recommendations for situations where concomitant treatment may not be excluded will also be considered. When a transporter has been identified that is likely to be involved in eribulin excretion, the SmPC will be updated to reflect the available

	performed within 12 months of licensing. - In vivo data supporting ketoconazole as a P-gp inhibitor will be presented and the issue of whether ketoconazole is less potent than the 3A4 inhibitors used in the clinical studies will be discussed within 6 months of licensing . The possibility of analyzing the clinical data to find out whether the use of the CYP3A4 inhibitors is likely to be due to an interaction, or if the increase in TEAEs may have other reasons will be investigated.	information. The possibility of analysing the clinical data to find out whether the use of the CYP3A4 inhibitors is likely to be due to an interaction, or if the increase in TEAEs may have other reasons will be investigated.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

In advanced stages of breast cancer the most important beneficial effects are increased overall survival (OS) in combination with a good tolerability of the drug, since this may impact the quality of the remaining time in life. Another important beneficial effect is prolonged progression-free survival (PFS), as time without tumour progression (and accompanying symptoms and psychological effects) are also of significant value for the quality of the remaining life.

The updated OS analysis showed consistent results with the original analysis, including HR 0.805 (95% CI 0.67, 0.96), p-value (0.014) and an increase of median OS from 75 to 82 days (2.7 months). In the Investigator assessment-based analysis of PFS the HR was 0.76 (95% CI 0.64, 0.90).

Since eribulin is a tubulin-targeting drug, the issue of cross-resistance between eribulin and other tubulin-active drugs was investigated. The positive effect on OS and PFS was seen in both taxane-refractory and non-refractory groups of patients. In the OS update, the HR for eribulin versus TPC was 0.90 (95% CI 0.71, 1.14) in favour of eribulin for taxane-refractory patients and 0.73 (95% CI 0.56, 0.96) for patients not taxane-refractory. In the Investigator assessment-based analysis of PFS (based on original data cut-off), the HR was 0.77 (95% CI 0.61, 0.97) for taxane-refractory patients and 0.76 (95% CI 0.58, 0.99) for patients not taxane-refractory.

A second subgroup of interest was the capecitabine-naïve patients. The positive effect on OS was seen both in capecitabine-naïve and in capecitabine pre-treated patient groups. The analysis of updated OS showed a survival benefit for the eribulin group compared to TPC both in capecitabine pre-treated patients with a HR of 0.787 (95% CI 0.645, 0.961), and for the capecitabine-naïve patients with a corresponding HR of 0.865 (95% CI 0.606, 1.233). Investigator assessment-based analysis of PFS (based on original data cut-off), also showed a positive effect in the capecitabine pre-treated group with a HR of 0.68 (0.56, 0.83). For the capecitabine-naïve group the corresponding HR was 1.03 (0.73, 1.45).

There were no important differences in terms of clinical efficacy with regard to HR point estimates and CIs for any of the sub-group analyses conducted.

Risks

- Unfavourable effects

Eribulin is eliminated mainly by biliary excretion and the transporter involved in unknown. If the biliary excretion is completely inhibited, this could result in a 250% increase in systemic exposure. A general warning is included in the SmPC but there may be inhibitors marketed where the inhibitory effect on the transporter is unknown. Further clarifications concerning transporter inhibition, hepatic impairment and renal impairment will be addressed in future studies, which are part of the risk management plan.

There are clearly more AEs and treatment-related AEs overall associated with eribulin treatment compared with TPC, and the pattern is consistent with that of a tubulin acting cytotoxic agent. With regard to the most frequent AE, asthenia/fatigue (occurring in >50% of patients), the difference was mainly due to grade 1-2 AEs, however. Most (3/4) cases of the other tubulin-inhibiting typical AE, peripheral neuropathy (occurring in around 35% of patients), were also grade 1-2. Even so, it was the AE most frequently causing treatment discontinuation, and the cumulative peripheral neuropathy is a factor likely to affect the quality of life during an extended time, possibly for the remainder of many patients' lives. The median Time to onset of peripheral neuropathy was 23 weeks in both pooled safety populations (AETP and BCP), and median Time to grade ≥ 2 peripheral neuropathy was 43 and 54 weeks, respectively. Time to resolution of peripheral neuropathy is not possible to assess with any degree of certainty, due to a large proportion of definitely censored patients, the most conservative estimation currently being 13 weeks, based on less than 20% being resolved. In the 32.5% of the BCP patients who experienced peripheral neuropathy events of CTC grade *higher than baseline* neuropathy, the event was resolved in 42% of cases, in the sense returning to baseline or lower. Twelve of 37 (32%) patients who discontinued treatment due to peripheral neuropathy resolved, as did 31/40 (77.5%) of patients who had their dose delayed or reduced due to peripheral neuropathy, indicating that peripheral neuropathy to some degree can be managed.

The incidences of neutropenia grade 3-4 and febrile neutropenia were high (45% and 4%, respectively), despite that one fifth of patients received G-CSF. A shift in absolute neutrophil count from grade 0 to 4 in cycle 1 was seen in 15.5% of patients. Neutropenia did not cause treatment discontinuation in high frequency however, and the impact on quality of life from a hospitalization due to such an event is normally of short duration. The long-term impact on bone marrow function and resulting increased risk of neutropenia is a problem shared with many classes of cytotoxic agents.

The incidence of nausea and vomiting is similar to that of other drugs used in this indication, as shown by the TPC-arm of Study 305, and may be controlled by anti-emetic premedication.

The incidence of thromboembolic SAEs (pulmonary embolism and deep vein thrombosis) is around what may be expected in this disease and therapy setting. The TEAEs with an outcome of death unrelated to disease progression was low (<1%), and a majority of these AEs were infections, as can be expected of immunosuppressive agents like eribulin.

In the BCP 12% of the patients received anti-emetics as treatment for adverse reactions during cycle 1, and 46% received anti-emetic prophylaxis, which in 1/2 of the cases included the corticosteroid dexamethasone. The incidence of nausea/vomiting in the subgroup of patients who did not use antiemetic during cycle 1 (42% of all patients) is consistently lower compared with the subgroups who used anti-emetics, most likely reflecting an enrichment in the anti-emetic treated groups of patients with current or previous nausea/vomiting reactions and consequent increased risk of these AEs. Thus,

the treating physicians appear to have successfully identified a patient population at risk of nausea and vomiting, and the "natural" incidence of these adverse events is likely to have been even higher if left without anti-emetic prophylaxis. It does appear, however, that the prescribers can handle this situation wisely. The frequencies reported in the BCP of 36% treatment-related nausea, and 14% treatment-related vomiting would motivate antiemetic premedication with one dose of corticosteroids, according to international recommendations. While corticosteroid anti-emetic prophylaxis may not be required for all patients, it should be considered.

There is a difference in the frequency of psychiatric disorders, 12 % in the TPC arm vs. 19% in the eribulin arm, and 22% in the pooled eribulin populations. The difference appears mainly to be driven by the preferred terms depression at 5 vs. 1% (additionally supported by depressed mood, mood altered, and mood swings) and insomnia at 8 vs. 4%. Some explanations for these differences have been given by the Applicant, including corresponding differences in the patients' histories of psychiatric disorders (17% vs. 14%, in the eribulin and TPC arms, respectively), and in baseline symptoms of depression (7.7% vs. 4.7%) and insomnia (8.9% vs. 6.7%). The overall frequency of baseline psychiatric disorders was 38.6% in the BCP population, and in Study 305 it was 33.0% in the eribulin arm and 28.3% in the TPC arm. The Applicant has also shown that the risk of experiencing psychiatric AEs is higher in patients with a history of psychiatric disorders.

- Uncertainty in the knowledge about the unfavourable effects

The pharmacokinetics of eribulin is presently not fully characterised. The main pathway of elimination is biliary excretion and at present there is no information on which transporter(s) is involved in the process making predictions of drug-interactions resulting in increased eribulin exposure impossible to perform. If the biliary secretion is completely inhibited, the exposure (AUC) could increase by 250%. CYP3A4 is an important drug metabolising enzyme. *In vitro* data indicate that eribulin may inhibit CYP3A4 in the liver. No *in vivo* data is available. If eribulin inhibits the enzyme significantly *in vivo*, this may lead to interactions with a number of drugs. The potential for drug-drug interactions is adequately reflected in the SmPC. Drug-drug interaction studies are being conducted (see 2.7 Risk Management Plan)

The potential risk for cardiac arrhythmias has not been adequately evaluated. Inhibition of IKr (hERG) *in vitro* was evaluated at a single concentration (30 µM). Therefore it is not possible to calculate an EC50 value for the estimation of safety margins. No QT prolongation was seen in conscious dogs but the highest tested dose (0.04 mg/kg) resulted in an exposure that was lower than the clinical. Furthermore, the dogs were given eribulin as a 60 min infusion, which probably made the difference in Cmax, i.e. the most relevant parameter to compare, larger still.

ECGs and QTc intervals were evaluated in the clinical Study 110. There were no signs of QT prolongation associated with the administration of eribulin, but as eribulin is a cytotoxic drug the study was not optimal to exclude such effects. Adequate information on QT prolongation is reflected in the SmPC (see section 4.4)

Time to resolution of peripheral neuropathy is not possible to assess with any degree of certainty, due to the high degree of censoring, > 80% of affected patients, only a few of whom still remained on therapy with ongoing neuropathy. While some information is available in the majority of patients who experienced peripheral neuropathy events of CTC grade higher than baseline (see previous section), the average Time to resolution and the proportion of the patients in whom the AE can be expected to resolve after discontinuation will not be known based on the present studies. There are however other ongoing studies that might shed more light on this issue, i.e. the randomised phase 3 Study 301

(E7389-G000-301), and the phase 2 Study 209 (E7389-G000-209), designed to specifically address the neuropathy safety issue (see section 7.7, Risk Management Plan).

Benefit-risk balance

- Importance of favourable and unfavourable effects

Considering that the comparator is chosen to be the most active and suitable for each individual patient, based on tumour characteristics and medical history, the magnitude of the OS results are considered clinically meaningful. Prolonged PFS is also of significant value to patients with incurable cancer and supports the survival findings.

Overall, the known toxicity and tolerability profile of eribulin is considered reasonably well characterised and in essence typical for cytotoxic drugs with this mechanism of action.

- Benefit-risk balance

In patients with advanced breast cancer, the benefits from eribulin in form of prolonged survival and progression-free survival are considered clinically relevant.

The incidence of neutropenia/febrile neutropenia was high and associated with cases of deaths. However, these are not considered to outweigh the benefits of treatment in terms of overall survival.

The nausea and vomiting reactions are seen with many cytotoxic compounds, and normally accepted when balanced against the beneficial effects. The frequencies in the present populations would suggest the use of corticosteroid anti-emetics according to internationally accepted guidelines. While corticosteroid anti-emetic prophylaxis may not be required for all patients, it should be considered.

Concerning peripheral neuropathy, this is an inherent problem with tubulin-targeting drugs, which can be acceptable in light of the benefits. The frequencies were not higher than for some other approved drugs, and the majority 3/4 of the events were grade 1-2. Robust data regarding Time-to-resolution of peripheral neuropathy will not be generated by the present studies, but other studies are ongoing, including one that specifically addresses this issue as primary objective (see section 2.7).

Remaining uncertainties concerning cardiac safety are part of the Risk Management Plan as an identified risk and addressed in PSURs.

In conclusion, the balance of benefits and risks is considered positive.

2.8.1. Discussion on the benefit-risk balance

In late-stage cancer the main safety issue is tolerability, while low-frequency SAEs are of less importance. The tolerability of eribulin is lower than that of some other agents used in latter lines of the disease, but this is accompanied by a relevantly improved chance of prolonged survival, which can be assumed to outweigh the tolerability-problems in the eyes of many patients and their prescribing doctors. Some of the identified and uncertain risks can be managed through the SmPC; further clarifications regarding the risks can be provided with further studies included in the RMP (see section 2.7).

2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were

needed to investigate further some of the safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Halaven monotherapy

in 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.

was favourable and therefore recommended the granting of the marketing authorisation.