

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201532

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201532
Priority or Standard	Priority
Submit Date(s)	3/30/10
Received Date(s)	3/30/10
PDUFA Goal Date	9/30/10, extended to 12/30/10 (due to a major amendment submission)
Division / Office	DBOP/OODP
Reviewer Name(s)	Martha Donoghue, M.D.
Review Completion Date	8/31/10
Established Name	Eribulin mesylate
(Proposed) Trade Name	Halaven
Therapeutic Class	Microtubule Inhibitor
Applicant	Eisai Inc.
Formulation(s)	1.0 mg/2 mL single use vial
Dosing Regimen	1.4 mg/m ² intravenously on Days 1 and 8 of a 21-day cycle.
Indication	Treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two

Intended Population(s)

chemotherapeutic regimens,
including an anthracycline and a
taxane.

Adults > 18 years of age

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends approval of new drug application (NDA) 201532 for the use of eribulin mesylate injection for the treatment of patients with metastatic breast cancer who have received an anthracycline, a taxane, and at least two prior chemotherapeutic regimens in the metastatic setting.

This NDA is primarily supported by a single multicenter open-label randomized controlled trial in patients with refractory breast cancer, Study E7389-G000-305 (Study “305”). Study 305 enrolled a total of 762 patients with locally recurrent or metastatic breast cancer who had received two to five prior chemotherapy regimens, including an anthracycline and a taxane. In addition, enrolled patients experienced disease progression within six months of their most recent chemotherapy and received a minimum of two prior chemotherapy regimens in the metastatic setting. Patients were randomized (2:1) to receive eribulin (n=508) or a single agent therapy chosen by their physician (designated by the applicant as the “Treatment of Physicians Choice,” or “TPC” arm, n=254).

The assessment of benefit in this application is based on the primary endpoint of overall survival. This reviewer’s recommendation for approval is based on the review of the clinical data, which supports the conclusion that eribulin prolongs overall survival when compared to other single agent therapies that physicians would typically use in the refractory metastatic breast cancer setting. A statistically significant, clinically meaningful prolongation in overall survival was observed in patients randomized to receive eribulin; median overall survival was 13.1 months in the eribulin arm (95% CI: 11.8, 14.3), compared to 10.6 months in the control arm (95% CI: 9.3, 12.5), with a hazard ratio of 0.809 (95% CI: 0.660, 0.991; p-value: 0.041).

Study 305’s secondary efficacy parameter of objective response rate supported the utility of eribulin in the setting of refractory metastatic breast cancer. This study demonstrated an improvement in objective response rate in the eribulin arm which was statistically significant based upon independent review and investigator assessment. Based on the independent reviewer assessment, the objective response rate was 11.2% (95% CI: 8.6% to 14.3%) for patients randomized to receive eribulin and 3.9% (95% CI: 1.9% to 7.1%) for patients in the TPC arm (p = 0.0006). Additionally, median progression-free survival was numerically prolonged by independent reviewer assessment but not statistically significant, but was (nominally) statistically significant by investigator assessment. Median progression-free survival by independent review was 45 days longer in the eribulin arm compared to the control arm [eribulin: 113 days (95% CI: 101,118), TPC arm: 68 days (95% CI: 63, 103); HR:0.865, (95% CI: 0.714,

1.048; $p = 0.137$]). Median progression-free survival by investigator review was 44 days longer in the eribulin arm compared to the TPC arm [eribulin: 110 days (95% CI: 100,114), control group: 66 days (95% CI: 60, 79); HR:0.757, (95% CI:0.638,0.900; $p = 0.002$)].

In addition, the applicant submitted supportive data from two single arm phase 2 studies in patients with locally advanced or metastatic breast cancer (studies E7389-A001-201 and E7389-G000-211) with primary endpoints of overall response rate that also demonstrated the activity of eribulin in the refractory setting. Overall response (all partial responses) based upon independent reviewer assessment was 11.5% (95% CI: 5.7% to 20.1%; median duration of response 171 days) and 9.3% (95% CI: 6.1% to 13.4%; median duration of response 126 days) in studies E7389-A001-201 and E7389-G000-211, respectively.

This reviewer acknowledges the inherent limitations of relying on the results of a single randomized, well-controlled study for approval; however, this reviewer concludes that that this submission provides sufficient scientific and legal bases for approval, as set forth in the Guidance for Industry, entitled "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.*" The guidance states that "reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible." Study 305 embodies many of the characteristics of a desirable single study described in the Guidance. It is a large, multicenter trial that demonstrated consistent results across most patient subsets, and achieved more than one endpoint. Furthermore, the demonstration of a clinically meaningful, statistically significant overall survival benefit in a refractory population that has very limited treatment options renders the conduct of a second confirmatory randomized control trial practically or ethically impossible.

This reviewer also notes that the results of Study 305, while clinically meaningful and statistically significant, are not substantially robust (with a p -value of 0.041). However, the updated overall survival data submitted by the applicant on July 28, 2010 corroborate the efficacy findings and strengthen the application.

1.2 Risk Benefit Assessment

Eribulin has been administered to 1,222 patients in open-label and active-controlled trials across multiple tumor types, including 240 patients who received eribulin therapy for 6 months or longer. Review of the safety database revealed that the profile of adverse events observed in patients treated with eribulin in Study 305 is consistent with that observed in other studies of eribulin.

The adverse events reported in 503 patients who received eribulin in Study 305 were typical of those observed with other cytotoxic agents that effect microtubule function, such as vinca alkaloids taxanes. The most common adverse reactions ($\geq 25\%$) reported in the 503 patients who received eribulin in Study 305 were asthenia/fatigue, neutropenia, alopecia, peripheral neuropathy, nausea, and constipation.

As reflected by the benefit in overall survival observed in patients randomized to the eribulin arm in Study 305, a lower percentage of patients died during or within 30 days of study treatment in the eribulin group (4.0%), compared to the TPC group (7.7%). Furthermore, the percentage of patients whose death was associated with a serious adverse event was also lower in the eribulin group (4.0% compared to 7.0%). Serious adverse events were experienced by approximately 25% of patients in both treatment arms, and the most common serious adverse reactions reported in eribulin-treated patients were febrile neutropenia (4%) and neutropenia (2%).

Among the 503 patients who received eribulin in Study 1, 106 (21%) developed Grade 3 neutropenia and 121 (24%) experienced Grade 4 neutropenia (according to adverse event reports submitted by the investigators). Eighty-one (16%) experienced severe neutropenia ($< 500/\text{mCL}$) lasting more than one week. Febrile neutropenia occurred in 23 (5%) patients and two patients died from complications related to febrile neutropenia. Dose reduction due to neutropenia was required in 62 (12%) eribulin-treated patients. The mean time to nadir within a cycle was 13 days and the mean time to recovery from severe neutropenia ($< 500 \text{ cells}/\text{mm}^3$) was 8 days. Grade 3 or greater thrombocytopenia occurred in 0.8 % of eribulin-treated patients. Patients with alanine aminotransferase or aspartate aminotransferase $> 3 \times \text{ULN}$ experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia than patients with normal aminotransferase levels. Patients with bilirubin $> 1.5 \times \text{ULN}$ also experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Among the 503 patients who received eribulin in Study 1, peripheral neuropathy occurred in 181 (36%), and was the most common toxicity leading to permanent discontinuation of eribulin. Fourteen patients (3%) required dose reduction due to peripheral neuropathies, 20 (4%) experienced any Grade peripheral motor neuropathy, and 8 (2%) patients developed Grade 3 peripheral motor neuropathy. Neuropathy lasting more than one year occurred in 27 (5%) patients. One hundred fourteen patients (23%) developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 20-657 days).

After careful review and analysis of the totality of data submitted with NDA 201532, this reviewer concludes that eribulin has an acceptable risk-benefit profile for patients with refractory metastatic breast cancer, a life-threatening disease. The 75 day improvement in median overall survival demonstrated in Study 305 is a reflection of safety as well as efficacy. In addition, the safety database demonstrates that the adverse events observed with eribulin therapy are relatively predictable, consistent with

drugs that have similar mechanisms of action, and manageable with surveillance, dose delays, and reductions.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Eribulin is indicated for the treatment of patients with life-threatening cancer. As such, no additional clinical post-marketing risk management activities are required at this time. The proposed USPI contains patient counseling information for prescribing physicians (oncologists) as well as a patient information leaflet.

1.4 Recommendations for Postmarket Requirements and Commitments

The Pediatric Review Committee granted a waiver of the requirements under the Pediatric Research Equity Act because the rarity of breast cancer in the pediatric population (0-18) renders conduct of the necessary studies impossible or highly impracticable.

At the time of completion of this review, proposed postmarketing requirements and commitments had not been communicated to the applicant. In addition, CMC review of the application had not yet been completed due to receipt of a substantial amount of new information from the Applicant on August 9, 2010. This submission was a major amendment, resulting in extension of the PDUFA deadline to December 30, 2010. Therefore, Sections 1.4.1 and 1.4.2 outline the postmarketing requirement and postmarketing commitments proposed by the clinical pharmacology and clinical reviewers, respectively.

1.4.1 Clinical Pharmacology Postmarketing Requirement

Using data submitted by the Applicant from six clinical pharmacology trials with rich PK data, FDA clinical pharmacology reviewers compared the pharmacokinetic data of patients with normal renal function to those of patients with mild and moderate renal impairment. This analysis demonstrated that the geometric mean dose-normalized AUC increased 2-fold in patients with moderate renal impairment. In addition, their analysis suggested a trend toward increased Grade 3-4 neutropenia and febrile neutropenia with increasing exposure. Based upon these findings, the following postmarketing requirement was proposed by the Office of Clinical Pharmacology:

Conduct a clinical trial to determine the pharmacokinetics and safety in patients with severe renal impairment. Refer to the FDA Guidance for Industry titled "*Pharmacokinetics in Patients with Impaired Renal Function*" for guidance with study design and data analysis.

The following timetable was proposed:

Final Protocol Submission: December 2010
Trial Completion Date: June 2012
Final Report Submission: December 2012.

1.4.2 Postmarketing Commitments

The clinical review team proposed two postmarketing commitments (PMCs). These commitments are proposed to obtain additional data regarding the OS effect size in patients treated with eribulin. The first proposed postmarketing commitment was for the submission of the final study report and datasets for overall survival for the registration trial, Study 305, after 95% of patient deaths (724/762) had been observed:

To submit final study report and datasets for overall survival for registration trial E7389-G000-305, "A Phase 3 Open Label, Randomized 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" after 724 patient deaths have been observed.

The following timetable was proposed based upon statistical simulation of the rate of patient deaths:

- **Trial Completion Date:** [REDACTED] (b) (4)
- **Final Report Submission:** **March 2013.**

Study 301, ongoing at the time of NDA submission, compares the efficacy of eribulin in with that of capecitabine in patients with advanced breast cancer. In order to obtain data that may help define the utility of eribulin in a less-heavily treated population, the following PMC was proposed:

To submit a final study report for ongoing trial E7389-G000-301, "A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes."

The following submission deadlines were proposed by the clinical reviewers:

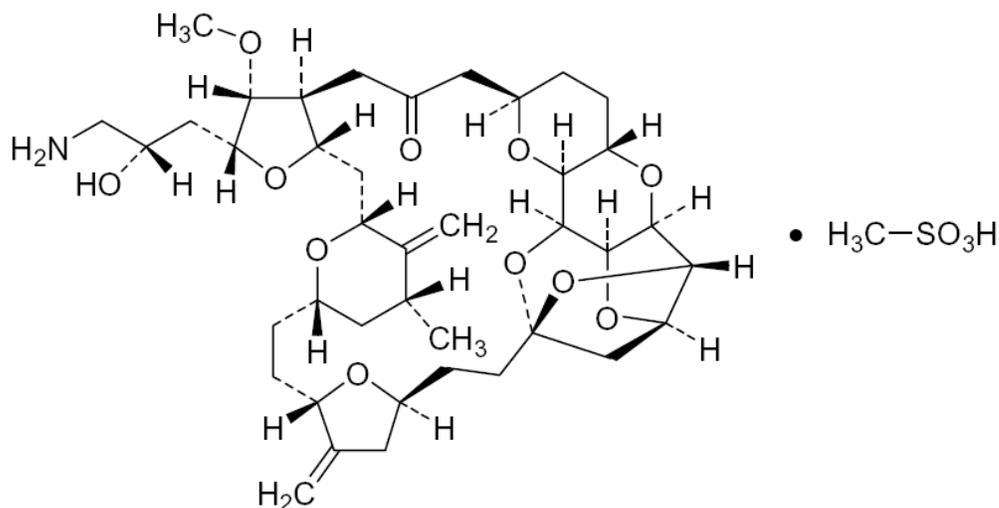
- **Trial Completion Date:** **by March 2011**
- **Final Report Submission:** **by February 2012.**

2 Introduction and Regulatory Background

2.1 Product Information

The proposed trade name for eribulin mesylate (eribulin) is Halaven. Eribulin injection is a microtubule inhibitor that disrupts mitotic spindles and promotes apoptotic cell death by inhibiting tubulin mitosis through blockade of the G₂/M cell cycle. In the NDA, the applicant indicated that eribulin inhibits the growth phase of microtubules without affecting the shortening phase, which results in the formation of nonproductive tubulin aggregates. The applicant asserts that this pattern of microtubule inhibition differs from other currently marketed tubulin-targeting agents, including the taxanes, vinca alkaloids, and epothilones.

The chemical name for eribulin mesylate is a 11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*l*] furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one, 2-[(2*S*)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2*R*,3*R*,3*aS*,7*R*,8*aS*,9*S*,10*aR*,11*S*,12*R*,13*aR*,13*bS*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29*aS*)-methanesulfonate (salt). It has a molecular weight of 826.0 (729.9 free base). The structural formula is illustrated below (copied from the NDA submission):



Eisai describes eribulin mesylate injection (eribulin) as a clear, colorless aqueous solution containing 0.5 mg/mL of drug substance in ethanol:water (5:95). The drug product is supplied in a single-use vial that contains 1.0 mg eribulin mesylate in 2 ml of solution. The drug product is intended to be administered intravenously without

dilution, but may be diluted in up to 100 mL with 0.9% sodium chloride prior to administration.

The proposed product label indicates that once withdrawn from the vial, Halaven can be stored in the syringe for up to 4 hours at room temperature or up to 24 hours under refrigeration. Diluted solutions of Halaven can be stored for up to (b) (4) hours at room temperature or up to 24 hours under refrigeration. Unused portions of the vial are to be discarded. The proposed labeling indicates that (b) (4)

Comment: CMC proposed changes to the proposed label submitted by the Applicant,, based upon review of CMC data included with this NDA. Text was added to clarify that Halaven should not be administered through an intravenous line with dextrose-containing solutions. Storage instructions were changed to allow storage of undiluted or diluted Halaven at room temperature for up to 4 hours (instead of (b) (4) for undiluted Halaven and (b) (4) hours for diluted Halaven proposed by the applicant) or refrigerated for up to 24 hours (instead of (b) (4) hours proposed by the Applicant).

For the treatment of patients with metastatic breast cancer, the proposed dosage is 1.4 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

2.2 Tables of Currently Available Treatments for Proposed Indications

The applicant proposed the following indication at the time of the original NDA submission:

(b) (4)

Table 1 and Table 2 list FDA-approved drugs for the treatment of patients with metastatic or locally recurrent breast cancer who have progressed following anthracycline and taxane-containing regimens. Other drugs administered to these patients include vinorelbine, cisplatin, carboplatin, etoposide, and rarely continuous infusion fluorouracil, and vinblastine with mitomycin.

Table 1: Currently Available Single Agent Treatments that are FDA-Approved for Locally Recurrent Or Metastatic Breast Cancer Refractory to Taxane And Anthracycline Chemotherapy

Drug	Class	Date of Approval	Specific Indication	Basis for approval
Capecitabine	Anti-metabolite	Accelerated Approval-1998	MBC resistant to paclitaxel and anthracycline-containing chemo regimens or resistant to paclitaxel and for whom further anthracycline therapy is not indicated	Response Rate (25.6%) in single arm study of 43 MBC patients resistant to paclitaxel and an anthracycline
Ixabepilone	Microtubule inhibitor	Regular approval - 2007	metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine	Objective response rate (12.4%) in 126 patients*

*Note: Approval of ixabepilone was based on the results of the study described in Table 2 supported by the ORR described in the single arm study.

Table 2: Currently Available Agents that are FDA-Approved Approved As Part of Combination Chemotherapy for Locally Advanced or Metastatic Breast Cancer Refractory to Taxane and Anthracycline Chemotherapy

Drug	Year of approval	Specific Indication	Basis for Approval
Ixabepilone + capecitabine	Regular approval - 2007	metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane	Improved PFS in a study of 752 patients with taxane and anthracycline resistant cancer comparing ixabepilone +capecitabine to capecitabine monotherapy

Drug	Year of approval	Specific Indication	Basis for Approval
Lapatinib + capecitabine	Regular approval 2007	advanced or metastatic breast cancer with over-expression of HER2 (ErbB2) after failure of an anthracycline, a taxane, and trastuzumab.	Improved TTP-comparing lapatinib+capecitabine with capecitabine monotherapy in 399 patients with HER2+ MBC who had been previously treated with anthracycline, taxane and herceptin.

Abbreviations: PFS: progression-free survival; TTP: time to progression

Table 3, Table 4, and Table 5 list drugs that are approved by FDA to date for the treatment of patients with metastatic breast cancer.

Table 3: Drugs Approved in First Line Metastatic Breast Cancer

Drug	Specific Indication	Date	Basis for Approval
Trastuzumab + paclitaxel	MBC with HER2 overexpression	Full approval 1998	Improved TTP supported by improvement in 12-month survival rates in the group receiving AC or paclitaxel + trastuzumab vs. chemotherapy alone in 469 patients with HER2+ MBC
Gemcitabine + paclitaxel	MBC after failure of prior anthracycline-containing adjuvant chemotherapy	Full approval 2004	Improved TTP supported by a strong trend toward improved survival in an interim analysis in a study of 520 patients with unresectable, locally recurrent or MBC comparing gemcitabine +paclitaxel with paclitaxel monotherapy
Lapatinib + letrozole	Postmenopausal women with HR+ MBC with HER2 overexpression and for whom hormonal therapy is indicated	AA 2010	Improved PFS of HER2+ group in randomized trial of lapatinib+letrozole vs placebo+letrozole as first line therapy in patients with HR MBC*

Drug	Specific Indication	Date	Basis for Approval
Bevacizumab+ paclitaxel	HER2- MBC who have not received prior chemotherapy	AA 2008	PFS improvement of 5.5 months with bev+paclitaxel compared to paclitaxel alone in single open label study of 722 patients; Not indicated for disease progression following anthracycline and taxane chemotherapy administered for metastatic disease

Abbreviations: AA: accelerated approval; PFS: progression-free survival; TTP: time to progression

*PFS in this group constituted the primary analysis

Table 4: Drugs Approved in Second and Third Line Metastatic Breast Cancer

Drug	Specific Indication	Date	Basis for approval
Paclitaxel	Treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated	Full approval 1994	Two arm study in 471 patients comparing TTP Paclitaxel 175 mg/m ² with Paclitaxel 135 mg/m ²
Docetaxel	2 nd -3 rd line metastatic breast cancer	AA 1996 Full approval 1999	3 phase 2 studies in 134 patients evaluating Overall RR Improved OS in a phase 3 study of 392 patients with prior anthracycline regimens comparing TTP and OS of docetaxel versus Mytomicin C+Vinblastine
Trastuzumab	Treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease	Full approval 1998	RR in single arm study of 222 MBC patients with HER2 overexpression and 1-2 prior chemotherapy regimens for MBC*

Drug	Specific Indication	Date	Basis for approval
Capecitabine + Docetaxel	Combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure or prior anthracycline-containing therapy	Full approval 2001	RCT of 511 patients with anthracycline-resistant MBC demonstrating statistically significant improvement in TTP, OS, PFS in patients treated with capecitabine + docetaxel compared to docetaxel monotherapy
Nanoparticle Paclitaxel 505(b)(2) application	Treatment of MBC after failure of anthracycline-containing combination chemotherapy for metastatic breast cancer or relapse within six months of adjuvant chemotherapy.	Full approval 2005	Improvement in Objective Response Rate in RCT of 460 patients with MBC receiving nanoparticle paclitaxel compared to paclitaxel

Abbreviations: AA: accelerated approval; RR; response rate; MBC: metastatic breast cancer; RCT: randomized controlled trial; TTP: time to progression; OS: overall survival
 PFS: progression-free survival;

*Approval of trastuzumab was based on improved TTP (in patients receiving first-line treatment) in a randomized controlled study supported by the results of the single arm study described in the table.

Table 5: Other Drugs Approved for Metastatic Breast Cancer

Drug	Date
Methotrexate	1953
Cyclophosphamide	1959
Thiotepa	1959
Vinblastine	1961
5-Fluorouracil	1962
Doxorubicin	1974

A clinically meaningful prolongation of overall survival is the preferred basis for drug approval in the treatment of metastatic breast cancer, because improved survival reflects both safety and efficacy (deaths are caused by toxicity or progressive disease, or both). Furthermore, overall survival is an unequivocal, direct measurement of clinical benefit. Overall survival has also been the basis of regular approval in the second line metastatic breast cancer setting (docetaxel monotherapy and capecitabine plus docetaxel). Time to progression was the basis of approval for paclitaxel and lapatinib in the second and third line treatment of MBC. Progression-free survival has been used as the basis for accelerated approval in first line metastatic breast cancer, and for the regular approval for ixabepilone in the third line setting. In the In the

December 5, 2007 and July 20, 2010 ODAC meetings, members discussed the use of PFS for the approval of drugs intended to treat women with breast cancer. In these meetings, committee members indicated that the magnitude of PFS prolongation was an important consideration in the determination of whether an improvement in PFS would be considered a clinical benefit.

There are no approved alternatives for patients with metastatic or locally advanced breast cancer for whom therapy with an anthracycline, a taxane, capecitabine and ixabepilone has failed.

2.3 Availability of Proposed Active Ingredient in the United States

Eribulin mesylate is a new molecular entity and is not currently marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

Eribulin is the first drug in the halichondrin class of antineoplastic drugs to be submitted for approval. However, there are several other approved chemotherapeutic agents that exert an effect through alteration of microtubule function. These drugs include the taxanes (paclitaxel and docetaxel), vinca alkaloids (vincristine, vinblastine, vinorelbine and vindesine), and the epithilone ixabepilone. Peripheral neuropathy and myelosuppression are common adverse effects associated with the taxanes and vinca alkaloids.

Important Safety Issues for the Vinca Alkaloids and Taxanes are summarized in Table 6 below.

Table 6: Important Safety Issues for Vinca Alkaloids and Taxanes

Warning	Boxed Warning?	Comments
Tissue extravasation injury	Y (vinca alkaloids)	May be severe and cause cellulitis, phlebitis, and skin sloughing.
Fatalities with intrathecal use	Y (vinca alkaloids)	Immediate neurosurgical intervention required to prevent life threatening ascending paralysis leading to death. Few patients survive; those that do have severe neurologic sequelae.

Warning	Boxed Warning?	Comments
Cytopenias	N	Granulocytopenia more common with taxanes and vinblastine; less common with vincristine. Anemia, thrombocytopenia may also occur. Monitoring for cytopenias at regular intervals recommended.
Gastrointestinal	N	Vincristine, Vinblastine: Constipation is common; ileus, hemorrhagic enterocolitis, intestinal necrosis and/or perforation can occur. Paclitaxel/Docetaxel: mucositis
Neurologic	N	(Vinca alkaloids) Paresthesias, loss of deep tendon reflexes, peripheral neuritis, mental depression, foot drop, ataxia, paralysis, and convulsions can occur. Rare vestibular and auditory damage to eighth cranial nerve. Use caution if used with other ototoxic agents. Jaw pain is common. Taxanes: peripheral sensory and motor neuropathies
Cardiac	N	(Vinca Alkaloids) Hypertension common. Myocardial infarction and cerebrovascular accidents in patients undergoing combination chemotherapy with bleomycin, cisplatin. Paclitaxel: rare severe conduction abnormalities
Hepatic	N	Toxicity may be enhanced in patients with hepatic insufficiency for both vinca alkaloids and taxanes
Hypersensitivity	Y (taxanes)	Rare anaphylaxis with vinca alkaloids.
Hepatic	N	(Vincristine) Veno-occlusive disease, particularly in pediatric patients; can be fatal or require liver transplantation
Endocrine	N	(Vincristine) Rare instances of syndrome of inappropriate antidiuretic hormone secretion.
Fluid retention	Y	Paclitaxel
Pulmonary	N	(Vincristine) Acute shortness of breath and bronchospasm, most frequently encountered with mitomycin-C

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 7 summarizes the key regulatory activities related to this submission.

Table 7: Key Regulatory Activities for NDA 201532

Date	Nature of Regulatory Activity	Issues
3/31/2003	IND submission	<ul style="list-style-type: none"> IND 67,193 submitted by Eisai
9/2/2005	EOP2 meeting	<ul style="list-style-type: none"> FDA determined that the population of patients who have received at least 2 therapies but no more than 4 (Her2+ patients must have received trastuzumab) represented an unmet medical need (<i>comment: see 12/14/2007 comments regarding change in the definition of a patient population with unmet medical need based on new available therapy (ixabepilone); FDA warned Eisai that the definition could change during the meeting</i>). FDA stated that the proposed ORR of (b) (4) was not of sufficient magnitude for AA. FDA stated that the acceptability of PFS as an endpoint in Study 301 would depend upon the magnitude of the difference and tolerability profile of E7389. FDA indicated that an independent review of radiographs would be necessary to use PFS as the primary endpoint. FDA emphasized that Study 301 should be powered to demonstrate an improvement in OS.
2/28/2006	IND letter regarding SPA	<ul style="list-style-type: none"> A SPA agreement was reached for Study 301
3/7/2006	Faxed Communication to Eisai	<ul style="list-style-type: none"> FDA determined that the non-clinical data package appeared adequate to support an NDA. FDA stated that EFD studies in rabbits were not necessary if rat studies demonstrated an effect on fetal development. FDA advised Eisai to conduct organ dysfunction and drug-drug interactions studies during drug development.

Date	Nature of Regulatory Activity	Issues
4/14/2006	Type B CMC Meeting	<ul style="list-style-type: none"> • Discussion held with Eisai regarding starting materials use in the manufacturing process. • FDA emphasized that the currently defined starting materials were not acceptable. • Eisai stated an intent to submit accelerated stability data for drug substance.
1/22/2007	Faxed Communications of FDA Answers to Eisai Submission	<ul style="list-style-type: none"> • FDA emphasized that HER-2 positive patients should receive prior treatment with trastuzumab. • FDA expressed concern that study 305 may not support full approval because the use of different therapies in the control arm would make it difficult to determine whether the toxicities of the control arm had an adverse impact on survival. • FDA recommended selecting a limited number of regimens for the control arm.
8/21/2007	Fast Track Designation	<ul style="list-style-type: none"> • FDA granted Fast Track Designation for the following: <ol style="list-style-type: none"> 1. Locally advanced or metastatic breast cancer refractory to or relapsed after treatment with standard therapy. 2. Eribulin demonstrates antitumor activity in patients with locally advanced or metastatic breast cancer refractory to or relapsed after treatment with standard therapy
8/23/2007	pre-NDA Meeting	<ul style="list-style-type: none"> • Agreements were made regarding the content of an NDA package based on the two single arm trials in refractory advanced breast cancer, studies 201 and 211. • FDA cautioned that the preliminary ORR of (b) (4) appeared low and that adequacy to support approval in a single arm study would be a review issue • FDA encouraged Eisai to proceed with the phase 3 trial, stating that regular approval of another drug for use in this population would block a subpart H approval for eribulin. .

Date	Nature of Regulatory Activity	Issues
12/14/2007	Telephone Conference	<ul style="list-style-type: none"> FDA stated that an NDA for AA based on response rate in a single arm trial would not be acceptable because eribulin was not better than available therapy (ixabepilone naïve population).
12/20/2007	Telephone Conference to Discuss Study 301	<ul style="list-style-type: none"> FDA stated that proposed changes to the SAP of study 301 (including the interim analysis of PFS and plan for a non-inferiority analysis of OS) were not acceptable and would render the SPA agreement invalid. Based on FDA advice, Eisai revised the SAP and FDA communicated concurrence with the changes on 5/13/2008.
3/21/2008	EOP2 Meeting Comments from FDA to Eisai	<ul style="list-style-type: none"> FDA expressed concern that study 305 may not be robust enough to support NDA approval and recommended that Eisai complete study 301 before submitting the NDA. The following review issues were communicated: whether TPC has an adverse impact on survival; whether the results of 305 alone would support approval. FDA requested clarification regarding whether appropriate patients received trastuzumab. Additional comments regarding DDI and QTc studies were described.
7/3/2008	Amendment to IND and Protocol 305	<ul style="list-style-type: none"> FDA agreed to a proposal to increase the sample size from 630 to 1,000 due to a smaller than expected event number (based on a pre-planned sample size reassessment). Target number of events remained unchanged (i.e. 411 deaths).
12/10/2008	Email to Eisai Re: Nov 21, 2008 Submission to IND	<ul style="list-style-type: none"> FDA recommend against an early interim administrative look at the data from study 305 to maintain blinding and the integrity of the study.
11/23/2009	Type B pre-NDA Meeting	<ul style="list-style-type: none"> FDA and Eisai reached agreements on the content of an NDA application

2.6 Other Relevant Background Information

2.6.1 Background Related to Advanced Breast Cancer

From 2003-2007, breast cancer occurred at an age adjusted-incidence rate of 122.9 per 100,000 women per year (SEER database, 2010). The incidence varied by age and race, with the highest incidence in women 75-79 of age in 2002-2006 (American Cancer Society Breast Cancer Facts and Figures, 2009-2010), and a higher incidence in Caucasian women compared to other races and ethnicities. The median age at diagnosis for breast cancer was 61 years of age (SEER database, 2010).

Survival of breast cancer patients can be variable depending on disease stage. The 5 year relative survival was 98% for patients with localized disease, 83.6% in patients with regional lymph node involvement, and 23.4% in distant metastatic disease (SEER database, 2010). Breast cancer among men is relatively rare, accounting for approximately 1% of all breast cancers (American Cancer Society Breast Cancer Facts and Figures, 2009-2010). Breast cancer in children is exceedingly rare; a recent article identified 75 patients less than 20 years of age who were diagnosed with malignant breast tumors between 1973 and 2004 based upon a review of the SEER database [Gutierrez JC et al. J Surg Res 2008 June 15;147 (2)].

2.6.2 Approval History of Drugs for Advanced Breast Cancer Refractory to Taxane and Anthracycline Therapy.

Table 8 describes the bases for the accelerated approval of capecitabine monotherapy and combination therapy with lapatinib, and the regular approval of ixabepilone for the treatment of patients with metastatic breast cancer who have received prior taxane and anthracycline therapy.

Table 8: Bases for Approval in Patients with Metastatic Breast Cancer Refractory to Anthracyclines and Taxanes

Drug	Initial Approval	Basis for Initial Approval
capecitabine	AA April 30, 1998	<ul style="list-style-type: none"> • RR in patients with measurable metastatic breast cancer that progressed after paclitaxel in a single noncomparative multicenter trial (n=135) • RR 18.5% (12.4, 26.1) with median duration of 154 days. • 25.6% RR with median duration of 154 days in patients with disease resistant to paclitaxel and anthracycline (n=43)

Drug	Initial Approval	Basis for Initial Approval
lapatinib + capecitabine	AA March 13, 2007	<ul style="list-style-type: none"> • TTP based upon prespecified interim analysis of a single randomized open label trial comparing lapatinib plus capecitabine to capecitabine monotherapy in patients with HER2 over-expressing locally advanced or metastatic breast cancer that progressed after treatment with anthracyclines, taxanes and trastuzumab (n=198 and 201) • Median TTP 27.1 (17.4, 49.4) and 18.6 (9.1,36.9) months, respectively. • HR 0.57 (0.43, 0.77) p value = 0.00013
ixabepilone monotherapy or combination therapy with capecitabine	Regular approval October 16, 2007	<ul style="list-style-type: none"> • PFS in open-label multicenter randomized trial comparing ixabepilone plus capecitabine to capecitabine monotherapy in patients with metastatic or locally advanced breast cancer that was resistant to or progressed after treatment with anthracyclines and taxanes. (n=375 and 377, respectively) <ul style="list-style-type: none"> • Median PFS 5.7 (95% CI, 4.8 to 6.7) and 4.1 (95% CI, 3.1 to 4.3) months, respectively • HR 0.69 (95% CI, 0.58 to 0.83) p<0.0001 • RR in multicenter single-arm study of 126 women with locally advanced or metastatic breast cancer after treatment with an anthracycline, a taxane and capecitabine. • RR 12.4% (95% CI, 6.9 to 19.9) in 113 evaluable patients

Abbreviation: AA: accelerated approval; RR; response rate; MBC: metastatic breast cancer; TTP: time to progression; PFS: progression-free survival;

Reviewer's note: Unlike this application, none of the approvals in the anthracycline and taxane-refractory population were based upon a demonstrated improvement in overall survival.

2.6.3 Evidence of Effectiveness from a Single Study

In the Guidance for Industry, entitled “*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*” published in May 1998, FDA described the circumstances in which the Agency would consider data from a single adequate and well-controlled study to provide a sufficient scientific and legal basis for approval. The Guidance allowing approval based on data from a single study was based upon the Food and Drug Administration Modernization Act of 1997. The guidance states that

“reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.” The guidance further described the following desirable characteristics that would support adequacy of a single study:

- Large multicenter study in which no single site provided an unusually large fraction of patients and no single site or investigator was disproportionately responsible for the effect on efficacy (that is, the study should generally have internally consistent results across sites)
- Consistency across relevant study subsets
- Multiple studies in a single study, such as those that provide multiple comparisons that demonstrate the activity of a drug as monotherapy and in combination with another drug.
- Statistically persuasive evidence of an effect on more than one relevant, prospectively identified endpoint
- Statistically very persuasive finding, such as a very low p-value, that indicates that the result is highly inconsistent with the null hypothesis that a treatment effect is absent.

The guidance acknowledged that reliance on persuasive results from a single, internally consistent, multicenter study has limitations, stating that “even a strong result can represent an isolated or biased result.” The guidance emphasized that it was important to consider “inadequacies and inconsistencies in the data” in the determination of whether a single trial is adequate to support approval.

This reviewer acknowledges that the inherent limitations of relying on the results of a single, randomized, well-controlled study for approval; however, this reviewer concludes that that this submission provides sufficient scientific and legal basis for approval. Study 305 embodies many of the characteristics of a desirable single study described in the Guidance document. It is a large, multicenter trial that demonstrated consistent results across most patient subsets, and achieved more than one endpoint (statistically significant improvement in ORR by independent review and nominally statistically significant improvement in PFS by investigator review). The demonstration of a statistically significant, clinically meaningful improvement in overall survival, an endpoint that is much less prone to bias, provides substantial evidence of clinical benefit. Furthermore, the demonstration of an overall survival benefit in this heavily pretreated population that has limited treatment options renders the conduct of a second confirmatory randomized control trial practically or ethically impossible.

This reviewer also notes that the results of Study 305, while clinically meaningful and statistically significant, are not substantially robust (with a p-value of .041). However, the updated overall survival data submitted by the applicant on July 28, 2010 corroborate the efficacy findings and strengthen the application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA submission was of adequate quality to allow for the review to be conducted. The following items were identified as impediments to the conduct of a timely review:

- Some adverse events were not graded using CTCAE criteria. Instead, they were coded as mild, moderate, or severe.
- There were multiple duplicate copies of many CRFs.

3.2 Compliance with Good Clinical Practices

All study reports submitted to the NDA contained a statement that the trial was conducted or is being conducted (for ongoing trials) in accordance with the Declaration of Helsinki and Good Clinical Practice. Eisai supplied audit certificates for applicable study sites that were audited. The applicant submitted case report forms (CRFs) for 249 patients enrolled in Study 305. Twenty-five percent of these case report forms were audited during the clinical review to determine if demographic and adverse event information contained in the datasets were accurate reflection of the records documented in the CRFs. All adverse events in the database were audited in this review; certain demographic data were also audited. Refer to section 7 of this review for a discussion of database/CRF audit findings regarding adverse events. In general, demographic data contained within the CRFs matched the data in the dataset.

3.2.1 DSI Inspections

Five clinical sites were chosen for inspection based upon the number of patients enrolled, number of protocol deviations, and differential response rate between the eribulin and TPC arms. DSI conducted inspections of two U.S. and three non-U.S. sites. DSI also inspected the records of the applicant (Eisai Europe Ltd., Hatfield, Hertfordshire, AL UK) and the clinical research organization contracted to provide support to Study 305 ((b) (4)). Table 9 shows the sites selected for inspection. Final results of DSI inspection were pending at the time of completion of this review. However, DSI staff communicated that no major issues had been identified from audits of the clinical sites as of August 19, 2010; however, voluntary action was indicated at a few sites. Please see the final DSI review for details regarding the DSI inspection results and recommendations.

Table 9: Clinical Sites Inspected for Study 305

Site/Clinical Investigator/Location	Number of Subjects	Preliminary Inspection Results
Site 2815 Dr. Joanne L. Blum US Oncology Dallas, TX	21	results pending
Site 2008 Dr. Javier Cortes Hospital Vall d'Hebron Barcelona, Spain	34	results pending
Site 2812 Dr. Han A. Koh Kaiser Permanente – Bellflower Bellflower, CA	18	results pending
Site 1401 Dr. Philippe Bougnoux Hopital Bretonneau Tours Cedex, France	17	results pending
Site 1402 Dr. Thierry Delozier Centre Francois Baclesse Caen Caen Cedex, France	19	results pending

3.2.2 Protocol Violations Study

Inclusion/Exclusion

A review of Study 305 conducted by Eisai revealed 77 (10%) patients with deviations in inclusion/exclusion criteria; 44 (9%) patients treated with eribulin and 33 (13%) patients in the TPC group did not meet one or more inclusion/exclusion criteria. The most frequent protocol deviation was the enrollment of patients who were not refractory to the most recently administered chemotherapy (16 [3%] and 11 [4%] in the eribulin and TPC groups, respectively). In addition, 15 (3%) patients in the eribulin group and 9 (4%) patients in the TPC group received more than five prior chemotherapy regimens. Furthermore, 8 (2%) patients treated on the eribulin arm and 7 (3%) TPC patients had only received one prior regimen for locally recurrent or metastatic disease.

Table 10: Tabular Listing of Important Protocol Deviations in Study 305

Site	Patient	Deviation	Arm
2803	1003	did not receive prior anthracycline	eribulin
1409	1005	did not receive prior anthracycline or taxane	eribulin
1706	1011	did not receive prior anthracycline/not refractory to most recent chemotherapy	eribulin
1901	1012	did not receive prior taxane	eribulin
2815	1010	did not receive prior taxane	eribulin
1101	1008	not refractory to most recent chemotherapy	eribulin
1708	1002	not refractory to most recent chemotherapy	eribulin
2008	1001	not refractory to most recent chemotherapy	eribulin
2008	1015	not refractory to most recent chemotherapy	eribulin
2403	1003	not refractory to most recent chemotherapy	eribulin
2404	1020	not refractory to most recent chemotherapy	eribulin
2413	1004	not refractory to most recent chemotherapy	eribulin
2812	1007	not refractory to most recent chemotherapy	eribulin
2828	1006	not refractory to most recent chemotherapy	eribulin
1301	1010	not refractory to most recent chemotherapy regimen	eribulin
1301	1028	not refractory to most recent chemotherapy regimen	eribulin
1401	1004	not refractory to most recent chemotherapy regimen	eribulin
1401	1006	not refractory to most recent chemotherapy regimen	eribulin
1401	1017	not refractory to most recent chemotherapy regimen	eribulin
1904	1003	not refractory to most recent chemotherapy/did not receive previous taxane	eribulin
1403	1004	received 1 regimen for metastatic disease	eribulin
1601	1005	received 1 regimen for metastatic disease	eribulin
1906	1003	received 1 regimen for metastatic disease	eribulin
2082	1002	received 1 regimen for metastatic disease	eribulin
2815	1015	received 1 regimen for metastatic disease	eribulin
2829	1001	received 1 regimen for metastatic disease	eribulin
2829	1004	received 1 regimen for metastatic disease	eribulin
1901	1005	received 1 regimen for metastatic disease (no taxane or anthracycline)	eribulin
1103	1004	received more than 5 prior chemotherapy regimens	eribulin
1302	1005	received more than 5 prior chemotherapy	eribulin

Site	Patient	Deviation	Arm
		regimens	
1302	1013	received more than 5 prior chemotherapy regimens	eribulin
1303	1003	received more than 5 prior chemotherapy regimens	eribulin
1304	1001	received more than 5 prior chemotherapy regimens	eribulin
1604	1007	received more than 5 prior chemotherapy regimens	eribulin
1705	1011	received more than 5 prior chemotherapy regimens	eribulin
2003	1001	received more than 5 prior chemotherapy regimens	eribulin
2008	1012	received more than 5 prior chemotherapy regimens	eribulin
2304	1003	received more than 5 prior chemotherapy regimens	eribulin
2502	1006	received more than 5 prior chemotherapy regimens	eribulin
2819	1007	received more than 5 prior chemotherapy regimens	eribulin
2830	1003	received more than 5 prior chemotherapy regimens	eribulin
3011	1001	received more than 5 prior chemotherapy regimens	eribulin
3011	1002	received more than 5 prior chemotherapy regimens	eribulin
1401	1003	received anticancer treatment within 3 weeks of study enrollment	eribulin
1403	1001	received anticancer treatment within 3 weeks of study enrollment	eribulin
3005	1011	Received radiotherapy within 3 weeks of study treatment	eribulin
2405	1003	wrongly diagnosed with metastatic disease	eribulin
2302	1002	enrolled with brain metastases	eribulin
2702	1007	enrolled with brain metastases	eribulin
2815	1004	enrolled with brain metastases	eribulin
2812	1011	received anastrozole during study	eribulin
2814	1002	received megace during study	eribulin
2818	1005	received megace during study	eribulin
3001	1007	did not receive previous anthracycline	TPC
1402	1019	did not receive prior anthracycline	TPC

Site	Patient	Deviation	Arm
1901	1007	did not receive prior taxane	TPC
1405	1001	not refractory to most recent chemotherapy	TPC
1509	1004	not refractory to most recent chemotherapy	TPC
1703	1006	not refractory to most recent chemotherapy	TPC
1907	1001	not refractory to most recent chemotherapy	TPC
2001	1004	not refractory to most recent chemotherapy	TPC
2005	1002	not refractory to most recent chemotherapy	TPC
2413	1005	not refractory to most recent chemotherapy	TPC
2603	1006	not refractory to most recent chemotherapy	TPC
2911	1001	not refractory to most recent chemotherapy	TPC
1301	1011	not refractory to most recent chemotherapy regimen	TPC
1401	1013	not refractory to most recent chemotherapy regimen	TPC
1302	1014	received 1 regimen for metastatic disease	TPC
1805	1002	received 1 regimen for metastatic disease	TPC
2503	1002	received 1 regimen for metastatic disease	TPC
2505	1011	received 1 regimen for metastatic disease	TPC
2829	1006	received 1 regimen for metastatic disease	TPC
2904	1008	received 1 regimen for metastatic disease	TPC
2914	1003	received 1 regimen for metastatic disease	TPC
1301	1004	received more than 5 prior chemotherapy regimens	TPC
1302	1010	received more than 5 prior chemotherapy regimens	TPC
1405	1003	received more than 5 prior chemotherapy regimens	TPC
1705	1006	received more than 5 prior chemotherapy regimens	TPC
1706	1004	received more than 5 prior chemotherapy regimens	TPC
2205	1002	received more than 5 prior chemotherapy regimens	TPC
2701	1004	received more than 5 prior chemotherapy regimens	TPC
2815	1002	received more than 5 prior chemotherapy regimens	TPC
2818	1003	received more than 5 prior chemotherapy regimens	TPC
2002	1005	received anticancer treatment within 3 weeks of study enrollment	TPC
2815	1001	enrolled with brain metastases	TPC

Site	Patient	Deviation	Arm
2812	1010	received exemestane during study	TPC
2401	1002	received letrozole during study	TPC
2828	1001	received megace during study	TPC
1701	1001	not randomized	TPC
2815	1013	randomized twice: initially to TPC, then to eribulin group	TPC

Table 11: Protocol Deviations - Study 305

Deviation Category	Number of Violations (% patients)	
	Eribulin N=508	TPC N=254
No previous taxane or anthracycline	5 (1.0)	3 (1.2)
Not refractory	16 (3.0)	11 (4.3)
Chemotherapy or Radiation treatment within 3 weeks of enrollment	3 (0.6)	1 (0.4)
1 prior regimen for metastatic disease	8 (1.6)	7 (2.8)
Wrongly diagnosed with metastatic disease	1 (0.2)	0 (0.0)
Enrolled with Brain metastases	3 (0.6)	1 (0.4)
> 5 previous chemotherapy regimens	15 (3.0)	9 (3.5)
Randomization error ^a	0 (0)	2 (0.8)
Not allowed Concomitant Medication	3 (0.6)	3 (1.2)

^a patient 28151013 was screened and randomized to TPC, then subsequently returned and was re-screened and re-randomized by IVRS to eribulin. This patient is included in the TPC arm in the ITT population, excluded from the per protocol population, and included in the eribulin group in the safety population. Patient 17011001 was not randomized, but received TPC therapy.

Seventy-seven patients with deviations from inclusion /exclusion criteria were excluded from the per-protocol (PP) population (44 in the eribulin group and 33 in the TPC group). In addition, ten additional patients who were enrolled but did not receive treatment were excluded from the PP population.

In response to a request from the clinical review team, the applicant provided the following explanations to account for the high number of protocol violations:

“The correct interpretation of the inclusion criteria regarding chemotherapy regimens requires a substantial understanding of the medical therapy of advanced breast cancer. In particular, this relates to the way in which drugs are combined into regimens and the way that regimens may be changed in the course of treating a patient. Given the fact that regimens do not necessarily have clear terminations (trastuzumab, for example, may be continued even when the chemotherapy with which it is combined is chanted), the

site monitors were not expected to handle this question. During the study, the sites were encouraged and expected to communicate directly with applicant personnel for these issues. Based on the number of such deviations observed on final applicant review of the study data, this approach was adequate for management of the study.”

Reviewer comment: Given the large number of protocol violations of major inclusion and exclusion criteria, this reviewer disagrees with the applicant’s interpretation of regarding whether the approach to study monitoring was adequate with respect to ensuring that patients met inclusion criteria. However, the protocol violations were relatively evenly distributed between the two treatment arms. Therefore, this reviewer concludes that it is unlikely that these protocol deviations affected the overall study results, noting these occurred prior to randomization and demographics between arms were evenly distributed. The per-protocol analysis failed to show a statistically significant difference in overall survival (HR 0.812, 95% CI 0.650, 1.105; $p = 0.066$). However, the hazard ratio is similar to that of the ITT analysis (0.809), and the lack of statistical significance reflects the smaller number of patients and events in the per protocol population (675 patients versus 762). In addition, the applicant’s analysis in the PP population that included patients who received more than 5 chemotherapy regimens demonstrated a statistically significant improvement in overall survival ($p = 0.034$).

3.3 Financial Disclosures

Eisai submitted a Form 3454 for studies E7389-G000-305, E7389-G000-211, E7389-G000-204, E7389-A001-202, E7389-A001-201, E7389-E044-110, E7389-E044-109, E7389-E044-108. The form certified that Eisai had no financial arrangements with the listed clinical investigator for these studies. Eisai provided a list of investigators who certified that they had no financial conflicts of interest as defined in 21 CFR 54.2(a)(b) and (f).

Eisai provided a statement indicating that FDA Form 3455 does not apply to any investigators in the studies listed above. In addition, Eisai provided a list of investigators for whom the required financial information could not be obtained. For study 305, six sub investigators had left employment, four employees were included in the initial FDA 1572 but the site closed before signatures were obtained, and 1 person was no longer part of the medical team.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

This section summarizes issues relating to the safety and efficacy of eribulin identified by other review disciplines as of July 26, 2010. This summary should be considered partial and preliminary. Please refer to the respective discipline reviews for a full description of the issues identified during the course of the review process.

4.1 Chemistry Manufacturing and Controls

The following issues relating to the safety and efficacy of eribulin were identified by CMC reviewers as of August 9, 2010. This list should be considered a partial summary of certain pertinent CMC issues, because CMC review of the major amendment submission was ongoing at the time of completion of this review. Please refer to CMC reviews for a full description of CMC issues.

- The CMC review team disagreed with Eisai's designation of starting materials (b) (4). Due to the chemical complexity of the product and the potential for the formation of (b) (4) during production, (which could have a different level of activity or a different toxicity profile than the intended product), the CMC team reiterated that it was crucial for the designated starting materials be (b) (4) in the manufacturing process ((b) (4)). The CMC review team also instructed Eisai to define the qualitative and quantitative impurity profiles for these materials, and stated that the acceptance specification should include an identity test that is selective for the specific (b) (4). Eisai agreed to comply with these recommendations at a meeting to discuss this topic on July 2, 2010. Based upon the results of this meeting, CMC communicated the specific items of information that must be provided by Eisai no later than August 9, 2010 to support approvability of the application. In addition, the CMC team identified potential post-marketing commitments involving acceptance criteria and test methods for impurities, estimated yields for production of intermediates, results of in-process testing from the manufacturing of intermediates and characterization of the newly designated starting materials.
- CMC reviewers required revisions to the drug product specification to include a single set of criteria for product release and for use in the stability studies.

The following additional issues and requirements were communicated to the applicant on July 2, 2010:

Drug Substance

- CMC requested Eisai to provide justification with supporting data to validate the proposed identification test for intermediates

- Eisai was instructed to revise acceptance criteria for total impurities of each isolated intermediate to more closely reflect the actual batch data.
- Eisai was instructed to provide acceptance criteria and test methods for assay of each isolated intermediate.
- Eisai was instructed to revise the acceptance criteria for (b) (4) of the manufacturing process to reflect batch data.

Drug Product

- Eisai was instructed to propose a test, method, and acceptance criterion for (b) (4) content, with an appropriate validation study for the proposed method.
- Eisai was instructed to revise acceptance criteria for degradants and impurities and to tighten the acceptance criterion for pH from (b) (4)
- Eisai was instructed to revise the validation study for the HPLC method used to determine degradants and impurities

4.2 Clinical Microbiology

FDA review microbiology review of drug product quality dated August 9, 2010 revealed no microbiology-related deficiencies.

4.3 Preclinical Pharmacology/Toxicology

The proposed label includes a warning that eribulin is expected to cause fetal harm if administered to a pregnant woman, based upon findings of embryofetal toxicity and teratogenicity in developmental toxicity studies of animals who received eribulin. Therefore, Halaven is designated as Pregnancy Category "D." In addition, the label describes maternal splenic enlargement, decreased weight gain, and decreased food consumption in pregnant rats following eribulin administration. The proposed label also describes nonclinical toxicology studies in dogs and rats that suggest male fertility may be compromised by treatment with eribulin. Finally, the label includes information indicating that eribulin mesylate was positive in mouse lymphoma mutagenesis assays and was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

In repeat-dose toxicity studies in rats and dogs, bone marrow suppression, thymic and lymphoid tissue atrophy, testicular degeneration, focal areas of liver necrosis, and elevations in AST, ALT, and cholesterol were observed. Degeneration of the sciatic nerve was also observed in rats. In the 29-day dog study, and the chronic dog and rat studies, all animals were terminated at the end of a recovery period; therefore the toxicities noted in these study reports only represent those toxicities which persisted

throughout the recovery period. The pharmacology/toxicology reviewer concluded that there were no pharmacology/toxicology issues precluding approval of eribulin for the requested indication.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Eribulin belongs to the halichondrin class of antineoplastic drugs. Eribulin is a synthetic analog of halichondrin B (HalB), which is isolated from the marine sponge *Halichondria okadaei*. HalB is a large polyether macrolide that inhibits the growth phase of microtubules without affecting the shortening phase, resulting in sequestration of tubulin into nonfunctional aggregates. Eribulin causes apoptosis of cells through prolonged blockage of mitosis. The applicant indicates that eribulin retains activity in cancer cells that are resistant to taxanes due to either β -tubulin mutations or β -tubulin overexpression.

Reviewers note: there is no clinical data to indicate that eribulin is more effective than taxanes in patients with breast cancers that harbor a β -tubulin mutation or overexpress β -tubulin.

4.4.2 Pharmacodynamics

Eribulin has demonstrated antitumor activity in multiple human xenograft models.

A dedicated study was conducted to evaluate the effects of eribulin on QTc intervals in 26 patients with solid tumors who received the recommended dose. In the study, QTc prolongation was observed following the Day 8 dose. The maximum mean QTcF change from baseline (95% upper confidence interval) was 11.3 (18.2) ms. Eribulin's effect on the QT interval appears to be concentration-independent.

Based upon the consult review by QT Interdisciplinary Review Team (QTIRT), clinical pharmacology reviewers recommended inserting the following text into the Warnings and Precautions section of the label:

Eribulin causes QT prolongation by an unknown mechanism in a concentration-independent manner. Avoid eribulin in patients with congenital long QT syndrome. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval including Class Ia and III antiarrhythmics and electrolyte abnormalities. Correct hypokalemia or hypomagnesaemia prior to initiating eribulin and monitor these electrolytes periodically during therapy.

4.4.3 Pharmacokinetics

After intravenous infusion, eribulin distributes rapidly and has a prolonged elimination phase, with a mean terminal half life of approximately 40 hours. It has a large volume of distribution (43 to 114 L/m²) and low clearance (mean, 1.16 to 2.42 L/hr/m²). Eribulin exposure after the second and third weekly doses in the first cycle of therapy was comparable to exposure following the first dose; thus eribulin accumulation with weekly dosing does not appear to be a concern. Linear pharmacokinetics are observed with doses of 0.25 to 4 mg/m².

Eribulin is weakly bound to plasma proteins. The plasma protein binding of eribulin ranged from 49% to 65% in human plasma.

There do not appear to be major metabolites of eribulin. Unchanged eribulin was the major circulating compound in plasma following administration of ¹⁴C-eribulin to patients, and metabolite concentrations represented less than 0.6 percent of the parent compound. The major enzyme responsible for eribulin metabolism is cytochrome P450 (CYP3A4). An open label study evaluating the effect of ketoconazole, a CYP3A4 inhibitor, on the PK of eribulin in 12 patients with advanced solid tumors demonstrated similar AUCs when eribulin was administered in combination with ketoconazole compared to when it was administered alone; therefore, no drug-drug-interactions are expected with CYP3A4 inhibitors. Studies in human primary hepatocytes did not demonstrate induction potential for CYP1A, CYP2C9, CYP2C19, and CYP3A by eribulin. In addition, CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 activity was not significantly inhibited by eribulin at concentrations up to 5µM in pooled human microsomes. Furthermore, *in vitro* drug interaction studies indicated that eribulin did not inhibit drugs that were substrates of these enzymes.

In vitro assays indicated that eribulin is a substrate and weak inhibitor of the drug efflux transporter P-gp. Therefore, FDA clinical pharmacology reviewers recommended that the product label include a recommendation that clinicians exercise caution if Eribulin is administered to patients who are on medications that inhibit P-gp.

Eribulin is excreted primarily unchanged in feces. Population PK analyses of data collected from 340 patients did not demonstrate a clinically meaningful effect of gender, race, or age on the PKs of eribulin.

A PK study of eribulin in 18 patients with hepatic impairment demonstrated that the mean dose-normalized exposure to eribulin increased 1.8- and 2.8-fold in patients with mild and moderate impairment, respectively, compared to patients with normal hepatic function. Administration of eribulin at doses of 1.1mg/m² to patients with mild hepatic impairment and 0.7 mg/m² to patients with moderate hepatic impairment resulted in

similar exposure to eribulin as doses of 1.4mg/m² to patients with normal hepatic function. Based on these results, FDA clinical pharmacology reviewers recommended insertion of the following text into the Warnings and Precautions section of the product label:

A lower starting dose of 1.1 mg/m² is recommended for patients with mild hepatic impairment (Child-Pugh A) and of 0.7 mg/m² is recommended for patients with moderate hepatic impairment (Child-Pugh B). Halaven was not studied in patients with severe hepatic impairment; therefore, the use of Halaven is not recommended in these patients.

In patients with moderate renal impairment, the median dose-normalized systemic exposure increased almost 2-fold compared to that of patients with normal renal function. Based on these results, clinical pharmacology reviewers recommended insertion of the following text into the Warnings and Precautions section of the product label:

...a lower starting dose of 1.1 mg/m² is recommended for patients with moderate renal impairment. The safety of Halaven was not studied in patients with severe renal impairment.

4.4.4 Interdisciplinary Review Team for QT Studies (QTIRT) Consultation (Thorough QT Study Review)

The review team identified QTc interval prolongation in the dedicated QT study (E7389-E044-110). This study was an open-label, multicenter, single-arm dedicated QT study in which 24 patients with advanced solid tumors received 1.4 mg/m² of eribulin mesylate on days 1 and 8 of a 21-day cycle. The largest upper bound of the 2-sided 90% confidence interval for the change from baseline in the QTcF was 18 ms observed on Day 8. Based on this finding, the QTIRT recommended that the applicant conduct a hERG trafficking study for parent and relevant metabolites with concurrent positive controls and perform a non-clinical study to detect delay in distribution of eribulin to the myocardium. In addition, QTIRT recommended that the following text be included in the product label:

- **Warnings and Precautions:** “Eribulin causes delayed QT prolongation by an unknown mechanism. Avoid eribulin in patients with congenital long QT syndrome. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT interval including Class Ia and III antiarrhythmics and electrolyte abnormalities. Correct hypokalemia or hypomagnesemia prior to initiating eribulin and monitor these electrolytes periodically during therapy.”

- **Effects on QTc interval:** QTIRT recommended that the description of the findings of the dedicated QT study be changed to include the upper bound of the 95% confidence interval (8.2 sec) increase from baseline

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 12 lists the clinical trials submitted in support of the NDA application. Some studies were submitted as synopses or interim reports because they were ongoing. Data from study 305 serves as the primary basis for the efficacy evaluation. The supportive evidence of efficacy is provided in the integrated summary of efficacy, which was based upon pooled data from studies 305, 201, and 211. Only data from subjects who were treated with the same dose and schedule of eribulin proposed in the product label were used in the integrated efficacy analysis.

The integrated summary of safety (ISS) reflects pooled safety data from eribulin-treated subjects enrolled in the following studies conducted by Eisai:

- studies 101-103
- studies 108-110
- studies 201-202
- study 204
- study 211
- study 305

The ISS also includes summaries of ongoing studies 104, 207, 209, 221 and 301 conducted by Eisai. In addition, interim data from eight ongoing NCI-sponsored studies of eribulin for a total of 389 patients with a variety of cancer types (NSCLC, prostate cancer, bladder cancer, ovarian cancer, head and neck cancer, pancreatic cancer) were included in this submission.

Table 12: Listing of Clinical Trials Submitted to the NDA

Study Number/ Phase	Design	Disease	E/T	Dosing Regimen	C	Endpoints	Status
305/ 3	M,O,R	LRBC or MBC	E:508/ 503 TPC:254/ 247	1.4 mg/m ² IV D 1,8 q 21 days	TPC	Primary: OS; Other: PFS ORR, DOR, Safety	Completed - Primary study

Clinical Review
Martha Donoghue
NDA 201532
Eribulin mesylate/Halaven

Study Number/ Phase	Design	Disease	E/T	Dosing Regimen	C	Endpoints	Status
211/ 2	M,SA,O	Advanced or MBC	299/291	1.4 mg/m ² IV D 1,8 q 21 days	N/A	Primary: ORR by IRR Other: Inv ORR DOR, PFS and OS, PK	Complete- supportive study
201/ 2	M,SA,O	Advanced or MBC ¹	104/103 ¹	1.4 mg/m ² IV D 1,8 q 21 days	N/A	Primary: ORR by IRR Other: Inv ORR , DOR, PFS and OS, PK	Complete- supportive study
101/ 1	M,OL, DF	AST	33/32	0.25,0.5,0.7,1 or 1.4 mg/m ² D1,8 & 15 q 28 days	N/A	MTD, PK, tumor response and safety	Complete
102/ 1	M,OL, DF	AST	21/21	0.25,0.5,1,2, 2.8 or 4 mg/m ² D1 q 21 days	N/A	MTD, PK, tumor response and safety	Complete
103/ 1	S,OL	AST	6/6	2 mg D1; 1.4 mg/m ² D8 ²	N/A	PK, excretion, mass balance, metabolic pathway, safety and efficacy	Complete
105/ 1	S, OL, DE	AST	15/15	0.7, 1, 1.4 or 2 mg/m ² D1,8 q 21 days	N/A	MTD/DLT, preliminary efficacy, safety and tolerability, PK	Complete
108/ 1	M,OL	AST	17/17	1.4 (normal hepatic function) , 1.1 (mild hepatic impairment), or 0.7 mg/m ² (moderate hepatic impairment)	N/A	PK, efficacy, safety in hepatically impaired patients	Complete

Clinical Review
Martha Donoghue
NDA 201532
Eribulin mesylate/Halaven

Study Number/Phase	Design	Disease	E/T	Dosing Regimen	C	Endpoints	Status
109/1	S, OL, R, CO	AST	12/12	D1: E: 1.4 mg/m ² D15: Combo E:0.7 mg/m ² & K:200 mg or D1: E 0.7 mg/m ² , D2:K 200 mg and D15: E: 1.4mg/m ²	N/A	Influence of ketoconazole on PK, safety and tolerability	Complete
110/1	M, OL,	AST	31/26	1.4 mg/m D1,8 & q 21 days	N/A	Impact on QT/QTc, PK/PD PK profile, safety, tolerability, ORR	Complete
202/2	M,SA,O	Advanced NSCLC	106/103	1.4 mg/m ² D1, 8,15 q 28 days or 1.4 mg/m ² D 1,8 q 21 days	N/A	ORR, DOR, PFS, OS, safety and tolerability	Complete
204/2	M,O	HRPC	112/108	1.4 mg/m ² D 1,8 q 21 days	N/A	PSA response rate, duration of PSA response, PFS, ORR, DOR and safety	Complete
104/1b	M, OL, two arm with carbo	AST	53/52	E: 0.7,0.9,1.1 or 1.4 mg/m ² D 1,8 q 21 days; Carbo: dosed for AUC 5-6 mg/mL	N/A	MTD when combined with carboplatin, efficacy, safety and PK	Ongoing
207/2	M.O	Advanced sarcoma	120/119	1.4 mg/m ² D 1,8 q 21 days	N/A	12 week PFS, ORR, OS, Safety, PK	Ongoing
209/2	M,O,R E vs. I	Advanced BC	9/9	E: 1.4 mg/m ² D 1,8 q 21 days I: 32 or 40 mg/m ² q 21 days	I	Neuropathy AEs, vibration sensibility, safety, efficacy	Ongoing

Study Number/ Phase	Design	Disease	E/T	Dosing Regimen	C	Endpoints	Status
221/ 2	M,O	Advanced or MBC	84/81	1.4 mg/m ² D 1,8 q 21 days	N/A	ORR, DOR, Safety	Ongoing
301/ 3	M,O,R E vs Cap	Advanced or MBC	870/851	E: 1.4 mg/m ² D 1,8 q 21 days Cap: 1250 mg/m ² twice daily for two weeks q 21 days.	Cap	OS, PFS, ORR, QoL, DOR, Safety, PK/PD	Ongoing
NCI- 5730/ 1	O	AST	40/38	0.125 mg/m ² -2.9 mg/m ² D 1,8,15 q 28 days.	N/A	MTD, Safety, PK, activity	Complete

1. Only data from subjects who were treated with the same dose and schedule of eribulin proposed in the product label were included in the integrated efficacy and safety analyses.
2. C1D1: one IV dose of ¹⁴C-eribulin (2mg, approx. 80 to 90 µCi); C1 D8 and extension phase: unlabeled eribulin (1.4 mg/m²) D 1,8 q 21 days

Abbreviations: C: control; M: multicenter; O: open label DF: dose finding AST: advanced solid tumors; MTD: maximum tolerated dose; PK: pharmacokinetic PD: pharmacodynamic; E/T: enrolled/treated; HRPC: hormone refractory prostate cancer I: ixabepilone; E: eribulin K: ketoconazole DOR: duration of overall response Cap: capecitabine MBC: metastatic breast cancer LRBC: locally recurrent breast cancer TPC: treatment of physician's choice IRR: independent radiology review AEs: Adverse events ORR: objective response rate; DOR: duration of response; OS: overall survival; PFS: progression-free survival; QoL: quality of life D: day

5.2 Review Strategy

Safety and efficacy data, including clinical study reports, CRFs, and datasets, were reviewed for study 305, the only completed randomized clinical trial that was submitted to the NDA. Efficacy data from supportive, single arm studies 201 and 211 were reviewed to verify response rate and duration of response. The remaining studies were primarily reviewed to identify any important safety signals that did not emerge from the analysis of Study 305. Section 5.3 contains a detailed discussion of the design of study 305, and a review of the designs of studies 201 and 211. Other studies are also briefly described in section 5.3.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 E7389-G000-305

This NDA submission is primarily supported by results from a single study, E7389-G000-305 (study "305"), entitled:

The 'EMBRACE' Trial: Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389. A Phase 3 Open Label, Randomized 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.

This study is an industry sponsored multicenter study that was conducted in 135 sites in 19 countries. Sixty-four percent of patients were enrolled in North America, Western Europe, or Australia. Twenty-five percent of patients were enrolled in Russia and Eastern Europe, and the remaining 11 percent of patients were enrolled in Latin America and South Africa. Overall, approximately 19% of enrolled patients were enrolled in U.S. sites; 100 patients from the United States were randomized to receive eribulin and 46 U.S. patients were randomized to the TPC arm. The 305 study report contains data from the first patient visit on November 16, 2006 until the date of primary data cut-off, May 12, 2009.

Table 13 shows the dates that the initial protocol and each amendment were finalized. The following section describes the final design of study 305, with details regarding important protocol amendments outlined subsequently.

Table 13: Dates of Submission of Protocol and Protocol Amendments for Study 305

Protocol or Amendment	Submission Date
Original Protocol	26 April 2006
Amendment 1	08 August 2006
Amendment 2	04 January 2008
Amendment 3	05 June 2008
Amendment 4	03 March 2009

5.3.1.1 Objectives

The primary objective of the trial was "to compare the overall survival (OS) of patients treated with E7389 versus the TPC (including any single agent anti-tumor treatment of the investigator's choice and palliative treatment) in patients with locally recurrent or metastatic breast cancer (MBC) who had received two to five prior chemotherapy regimens, which must have included an anthracycline and a taxane as prior therapy and at least 2 of which must have been given for locally recurrent or metastatic disease. Patients must also have been refractory to their latest chemotherapy regimen, documented by progression on or within six months of therapy" (E7389 was used as an alternate name for eribulin in the investigational setting).

Comment: The use of a variety of agents in the control arm complicates the ability to compare the efficacy or safety of eribulin to that of any specific therapy used in refractory metastatic breast cancer. Because only 2 patients were enrolled with disease limited to local recurrence, conclusions regarding eribulin efficacy in the locally recurrent setting cannot be made.

Secondary objectives included comparison of progression-free survival (PFS) and objective tumor response rate (ORR) and duration of response in the two treatment groups. In addition, safety parameters, including adverse events, use of concomitant medications and study drug exposure were evaluated.

5.3.1.2 Inclusion and Exclusion Criteria (copied from the protocol with some modifications for brevity)

Inclusion Criteria

- Females with Histologically or cytologically confirmed carcinoma of the breast
- Locally recurrent or metastatic disease
- Receipt of 2-5 prior chemotherapeutic regimens for breast cancer
 - A minimum of two chemotherapy regimens had to be for locally recurrent and/or metastatic disease
 - Previous regimens must include an anthracycline and a taxane, unless contraindicated for the patients. These therapies could be in the neoadjuvant, adjuvant, or relapsed/metastatic setting.
- Patients must have progressed on or within six months of their most recent chemotherapy regimen
- Patients with HER2/neu positive tumors could have been treated with trastuzumab

Reviewers note: treatment of HER2/neu positive patients with trastuzumab was not required

- Patients could have additionally been treated with anti-hormonal therapy

Reviewers note: treatment of ER/PR positive patients with hormonal therapy was not required (in practice, patients with visceral disease may not be treated initially with hormonal therapy).

- Resolution of chemotherapy and radiation therapy related toxicities to Grade 1 or lower severity, except for stable sensory neuropathy \leq Grade 2 and alopecia.
- Age \geq 18 years
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2
- Live expectance \geq 3 months
- Adequate organ function as evidenced by:

- Serum creatinine ≤ 2.0 mg/dL (or calculated creatinine clearance ≥ 40 mL/min)
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L; hemoglobin (Hb) ≥ 10 g/dL; platelet count $\geq 100 \times 10^9$ /L
- Bilirubin ≤ 1.5 X upper limit of normal (ULN); Alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 X ULN (for patients with liver metastases, ≤ 5 X ULN)
- Willing and able to comply with the protocol and grant written informed consent prior to study-specific screening procedures.

Important Exclusion Criteria

- Receipt of any of the following treatments within the specified period before starting treatment with eribulin or TPC:
 - chemotherapy, radiation therapy, trastuzumab or hormonal therapy within three weeks
 - any investigational drug within four weeks
- Radiation therapy encompassing $> 30\%$ of marrow
- Prior treatment with mitomycin C or nitrosurea
- Pulmonary lymphangitic involvement that resulted in pulmonary dysfunction requiring active treatment, including the use of oxygen.
- Brain or subdural metastases, unless local therapy was completed and use of corticosteroids for this indication discontinued for at least four weeks prior to study therapy. Signs or symptoms of brain metastases must have been stable for at least four weeks prior to study therapy
- Meningeal carcinomatosis
- Patients on anti-coagulant therapy with warfarin or related compounds who could not be changed to heparin-based therapy if randomized to eribulin (except for mini dose warfarin for line patency).
- Pregnant or lactating
- Severe/uncontrolled intercurrent illness
- Significant cardiovascular impairment (NYHA CHF $>$ grade 2, unstable angina, myocardial infarction within the previous 6 months, serious cardiac arrhythmia)
- Requirement for immunosuppression for prophylaxis of organ allograft rejection
- Known positive HIV status
- Prior malignancy, other than previous breast cancer, carcinoma in situ of the cervix, or non-melanomatous skin cancer, unless diagnosed and definitively treated ≥ 5 years previously
- Preexisting neuropathy of $>$ grade 2 severity
- Hypersensitivity to Halichondrin B (HalB) or HalB chemical derivative
- Participation in prior clinical study of eribulin
- Significant disease or disorder that, in the Investigator's opinion, preclude patient enrollment

5.3.1.3 Protocol-Specified Study Discontinuation Criteria

Criteria for Patient Discontinuation from Study Treatment or Assessments

- Progressive Disease (PD) by clinical evaluation or radiological evaluation by RECIST Criteria
- Undue toxicity
- Withdrawal of consent
- Investigator conclusion that further therapy was not in the best interest of the patient.
- Presence of other medical conditions that prohibited therapy continuation
- Pregnancy
- Lack of patient compliance with study procedures that compromise safety, despite repeated efforts by the Investigator to contact the patient
- Delay of treatment by more than 14 days due to toxicity
- Termination of study by the Sponsor

5.3.1.4 Definition of Prohibited Concomitant Therapies

Patients Randomized to Receive Eribulin

- Other investigational drugs
- Anti-tumor therapies such as chemotherapy, hormone therapy (including Zoladex, Megace, irrespective of the reason they are given), radiation therapy (except for palliative), gene therapy, biologics, or immunotherapy
- Warfarin, unless mini-dose

Patients Randomized to Receive TPC

- Other investigational drugs
- Any other anti-tumor therapy that had not been identified as the TPC treatment at the beginning of the study
- Any drugs that are contraindicated for use with the assigned TPC treatment

5.3.1.5 Trial Design and Treatment Plan

- Study 305 is an open-label, multi-center, international randomized study comparing overall survival of patients with locally recurrent or metastatic breast cancer treated with eribulin with those treated with a single agent therapy chosen by their physician (TPC).
- In order to be eligible, patients must have received 2-5 prior chemotherapy regimens, including a taxane and an anthracycline. At least two chemotherapy regimens must have been administered in the metastatic or locally recurrent setting.
- 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

- Randomization was stratified based upon geographic region, HER2/neu status, and prior treatment with capecitabine.
- 762 patients were randomized on a 2:1 basis to receive either eribulin (1.4 mg/m² IV over 2-5 minutes on days 1 and 8 every 21 days) or TPC.
- Use of granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and erythropoietin was permitted.
- Antidiarrheal drugs, anti-allergic drugs, stable bisphosphonates, and limited palliative radiotherapy were permitted for eribulin-treated patients. Relevant instructions regarding concomitant therapy from package inserts of assigned TPC therapy were followed for patients randomized to the TPC arm.
- The dose of E7389 could be reduced or discontinued during any cycle according to toxicity. Doses that were reduced were not re-escalated.
- Recovery of ANC to $\geq 1.0 \times 10^9/L$ and platelets to $\geq 75 \times 10^9/L$, and improvement of toxicities incurred from previous cycles to \leq Grade 2 (except anemia and alopecia) were required for eribulin administration. If treatment was postponed, the first day of treatment was considered to be Day 1 of that cycle.
- If treatment was delayed by more than 2 weeks, patients were withdrawn from the study, unless the investigator agreed to allow the patient to remain on study
- Responding patients could remain on treatment for the duration of clinical benefit
- An independent data monitoring committee (DMC) reviewed safety and evaluated interim efficacy data.
- Eribulin dose was reduced to 1.1 mg.m² on Day 1 if one of the following occurred during the previous cycle:
 - Hematological Grade 3-4 toxicities, defined as
 - Grade 4 neutropenia lasting more than 1 week
 - Grade 3 or 4 neutropenia with fever or infection requiring treatment with growth factors or antibiotics
 - Platelets $< 25,000/mm^3$ or $< 50,000mm^3$ requiring transfusion
 - Non-hematologic Grade 3-4 toxicities in the previous cycle, recovered to \leq Grade 2 within 7 days, with or without maximal supportive care
 - Omission of Day 8 administration for toxicity.
- Eribulin dose was postponed on day 8 if hematological (ANC $< 1.0 \times 10^3/mm^3$ and/or platelet count $< 75 \times 10^3/mm^3$ or non-hematological (any $>$ Grade 2 except inadequately treated nausea and/or vomiting) toxicities occurred until recovery. If recovery occurred on or before Day 15, treatment resumed at a reduced dose of 1.1 mg/m². Otherwise, Day 8 treatment was omitted for that cycle and resumed on Day 1 of the next cycle.
- If hematological or non-hematological toxicities recurred despite dose reduction and use of growth factors or if Grade 3 or 4 non-hematological toxicities recurred, the dose was reduced to 0.7 mg/m².
- If Grade 3-4 toxicities recurred after 2 dose reductions, the patient was removed from study treatment.

- Administration and dose modification of TPC therapy was performed according to the product package insert or local practice.
- Tumor assessments were performed for all patients at 8-weekly intervals (+/- 1 week), irrespective of the arm they were randomized to.

Figure 1: Schedule of Assessments for Study 305 (copied directly from NDA submission)

Assessments	Screening	Treatment Cycle (days)			Study Termination	Follow-up
	Days -21 to 0	Day 1	Day 8	Day 15	Within 30 days of final treatment	Every 3 months
Informed Consent ^k	X					
Inclusion/Exclusion Criteria	X	X				
Demographic Data	X					
Medical/Surgical History	X					
Tumor Assessments (RECIST)	X ^a	X ^a			X	X ⁱ
ECOG Performance Status	X	X			X	
Physical Examination	X ^b	X	X	X	X	
Vital Signs	X	X ^c	X ^c	X ^c	X ^c	
12-Lead ECG ^d	X	X ^d			X	
Pregnancy Test (if applicable)	X ^e	X ^e				
Hematology, Chemistry	X	X ^{fg}	X ^{fg}	X ^{fg}	X	
Urinalysis	X	X			X	
E7389 Administration ^h		X	X			
Prior Medications and Procedures	X	X				
Concomitant Medications		Throughout				
Adverse Events		Throughout				
Survival information						X ^j

Schedule of Assessments for Study 305 (continued)

Footnotes: (modified slightly from protocol)

- a. Baseline tumor assessments with MRI or CT scans of the chest, abdomen, pelvis, and any other areas of suspected disease, as well as photographs of skin lesions being measured as target lesions, should be performed within four weeks prior to start of study treatment. Areas where disease was found at baseline will then be scanned/photographed every 8 weeks, +/- 1 week after the start of study treatment, or sooner if there is evidence of progressive disease. During the study, scans/ photographs are only required for areas where disease was defined at baseline, unless there is suspicion of disease at other sites. If patients discontinue from the study without Progressive Disease, tumor assessments should be performed at study termination (within 30 days of last study treatment administration) and then every 3 months until Progressive Disease or start of another anti-cancer therapy. Radio-isotope bone scan using 99m technetium-labeled polyphosphonate scintigraphy should be performed within 6 weeks before start of study treatment and will only be repeated during the study if clinically indicated.
- b. A complete physical exam will be done at Screening, Day 1 of each cycle, and at Study Termination. A symptom directed physical exam will be performed on Day 8 of every cycle, on Day 15 of the first 2 cycles, and on Day 15 of any future cycles if clinically indicated. Assessments scheduled on Day 1 of Cycle 1 may be performed within 72 hours prior to Day 1 of the Cycle 1 visit. Assessments scheduled on Day 1 of all other cycles and on Day 8 and Day 15 may be performed within 24 hours prior to scheduled visit.
- c. Weight measurement will be performed on Day 1 of each cycle and at Study Termination. Temperature, blood pressure, and heart rate will be measured on Day 1 and 8 of each cycle, and on Day 15 of Cycle 1 and 2. For cycles 3 and beyond, vital signs will be measured on Day 15 only when deemed necessary. Assessments scheduled on Day 1 of Cycle 1 may be performed within 72 hours prior to the Day 1 Cycle 1 visit. Assessments for Day 1 for all other cycles, Day 8, and Day 15 may be performed within 24 hours prior to the scheduled visit.
- d. ECG evaluations will be performed at Screening and at Study Termination for all patients. Patients randomized to eribulin will also have one ECG prior to starting the second cycle of eribulin. It is recommended to perform this ECG on Day 1 of Cycle 2 prior to E7389 dosing.
- e. Urine or serum pregnancy test at screening and pre-dose Day 1, first cycle only. If the screening pregnancy test is performed within 72 hours of Cycle 1, Day 1 dose.
- f. Review laboratory assessments prior to drug administration. Hematologic assessments include: red blood cell count, hemoglobin, hematocrit, platelet count, total white blood cell count with differential, and absolute neutrophil count. Chemistry measurements include: albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, calcium, chloride, creatinine, glucose (at screening only), lactate dehydrogenase, magnesium, phosphorous, potassium, total protein, and sodium. Cycle 1 Day 1 assessments may be performed within 72 hours of the Day 1 visit. Assessments for Day 1 for all other cycles, Day 8 and Day 15 may be performed within 24 hours prior to the scheduled visit.

- g. For \geq Grade 3 neutropenia or thrombocytopenia, repeat complete blood count with differential and adverse event assessment at least every 3 days until improvement to Grade 2 or less. Day 15 assessments will be performed for the first two cycles only, unless \geq Grade 3 neutropenia occurs in Cycle 1 or Cycle 2, or clinically indicated.
- h. For patients on the eribulin arm only.
- i. For patients who come off study for reasons other than progressive disease, disease evaluation should be done every 3 months from the last study evaluation.
- j. Survival information should be collected every 3 months until patient dies.
- k. Informed consent must be obtained prior to any study-specific procedures and within 21 days of initiation of therapy. Procedures performed as part of routine care and which occur prior to obtaining informed consent are acceptable only if they fall within the allowed period for scans (6 weeks for bone scans and 4 weeks for CT/MRI scans)

5.3.1.5 Statistical Design/Sample Size

The main efficacy endpoint for study 305 is overall survival, defined as the time from the date of randomization until the date of death from any cause, based upon the intent to treat (ITT) population. The ITT population included all patients who were randomized, irrespective of whether or not they received study medication. Patients who were lost to follow up were censored at the date the patient was last known to be alive for patients who were lost to follow-up prior to death. Patients who remained alive at the time of data cut-off (May 12, 2009), were censored at the data cut-off date for overall survival analyses.

Secondary objectives of the study were to assess PFS, objective response rate, and duration of response, based upon independent reviewer assessments. PFS, based upon the intent to treat population, was defined as the time from the date of randomization until PD or death from any cause, in the absence of progressive disease. Patients lost to follow up were censored at the last date of tumor assessment if treatment was discontinued for a reason other than PD or death, if a patient was lost to follow up, if the patient started a new cancer treatment, or if the patient was still without progressive disease as of the data cut-off date (May 12, 2009).

Response Evaluation Criteria in Solid Tumors (RECIST) were used to assess measurable disease. The objective response rate was defined as the number of patients with confirmed CR or PR divided by the number of patients in the analysis population. Duration of response was defined as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to any cause. The response evaluable population, which consisted of all patients with measurable disease per RECIST by independent review, was prespecified as the primary analysis population for objective response rate and duration of response.

Sample Size:

The original statistical analysis plan specified enrollment of 640 patients (420 in eribulin and 210 in TPC) based on an analysis of overall survival after 411 deaths occurred. Based upon a pre-specified interim assessment indicating that the number of patient deaths occurring within 15 months of enrollment of the first patient was fewer than expected, the sample size of 630 patients was increased to allow enrollment of up to a maximum of 1,000 patients

Data Analysis:

A pre-specified interim analysis was performed after 50% (206) of enrolled patients died. Based upon this analysis, study 305 could have been stopped early for superiority or lack of efficacy based on overall survival. Based upon the O'Brien and Fleming alpha spending function, the nominal significance level for the interim test was 0.003, and the nominal level of significance for the final analysis was 0.049. If improvement in overall survival in the eribulin arm achieved a p-value less than 0.003 at the time of the interim analysis, then the study was to be stopped for superior efficacy. Conversely, if the interim analysis demonstrated a hazard ratio in which the lower limit of the 95% confidence interval was higher than 0.85, the study was to be terminated for lack of efficacy.

Adverse Event Reporting:

Adverse events were graded either using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3, or characterized using the terms "Mild", "Moderate" or "Severe". Adverse events were to be monitored and recorded from the time of signing of the informed consent document until the patient termination visit, which occurred from 0-30 days after the final dose of study medication. Thereafter, follow-up was limited to survival and disease status, if applicable. Serious adverse events, regardless of causality, were collected through the termination visit or for 30 days following discontinuation of study drug, whichever was longer. An adverse event was considered treatment emergent if it began or worsened during or within 30 days after receipt of study medication. *Comment: this design for the collection of adverse events may have resulted in an underestimation of the incidence of certain adverse events. For example, if a patient developed late onset neuropathy that occurred more than 30 days after the final dose of study medication, the adverse event might not be reported.*

5.3.1.6 Amendments:

The original protocol was submitted April 26, 2006. Four amendments to this protocol were submitted between August 8, 2006 and March 3, 2009. The following paragraphs summarize the important aspects of each of the four amendments.

Amendment 1 (August 8, 2006):

This amendment incorporated an additional inclusion criterion requiring patients to be proven refractory to the most recent chemotherapy, documented by progression on or within six months of therapy. In addition, an exclusion criterion was made more stringent: patients were required not to have received chemotherapy, radiation therapy, trastuzumab, or hormonal therapy with within three weeks of study therapy (rather than one to two weeks). An additional exclusion criterion was added to prevent enrollment of patients who received any investigational therapy within four weeks of study therapy. This amendment also provided clarification that it was possible to enroll patients with non-measurable disease, because the primary endpoint was overall survival. An additional stratification factor based on prior capecitabine exposure was added to the randomization scheme.

Amendment 2 (January 4 2008)

This amendment enacted changes to allow screening procedures other than baseline tumor assessments to be conducted within 21 days prior to the start of study treatment, instead of 14 days. Photographs of skin lesions being measured as target lesions were added to the list of baseline tumor assessments. Megace and Zoladex were added to the list of prohibited concomitant medications. The amendment clarified that tumor marker levels were not sufficient to assess tumor burden, and that CT or MRI scans of the chest, abdomen, and pelvis and photographs of skin lesions were necessary at baseline. In addition, the amendment informed investigators that chest radiographs were not sufficient to assess the extent of disease in the chest.

Amendment 3 (June 5, 2008)

In this amendment, the cap on patient sample size was increased from 630 to 1000 patients to achieve the required number of deaths.

Amendment 4 (March 3 2009)

No clinically relevant changes were made to the protocol in this amendment.

5.3.1.6 Independent (Radiology) Review Charter

Independent radiology reviews were performed by an independent imaging core laboratory (b) (4)) to assess tumor response and progression. Data from 32 patients were re-read by the independent reviewers. In each case, the same radiology reviewer who performed the initial assessment performed the subsequent evaluation. The second radiological readings were performed for the following reasons: four of the duplicate readings occurred due to a (b) (4) system error; thirteen occurred because new clinical data affected the baseline selection of target lesions or the date of first dose (affecting the determination of best overall response); and new images performed prior to data cut-off that had previously

been considered irretrievable became available for fifteen patients. *Comment: A review of the impact of these “re-reads” demonstrated that they did not affect the results of the analyses.*

5.3.2 Supportive Studies for Efficacy and Safety

Two additional supportive studies investigating the efficacy and safety of eribulin in refractory metastatic breast cancer were submitted with this NDA, Study E7389-G000-211 (Study 211) and Study E7389-G000-201 (Study 201). Safety data from these studies provide additional data from 324 patients with advanced breast cancer who received the same dosage regimen as patients enrolled in Study 305:

Study 211

Study 211 is a phase 2, open-label, single arm study evaluating the safety and efficacy of eribulin in 299 patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine. In this study, 291 patients received the same dosage regimen as those randomized to receive eribulin in Study 305 (1.4 mg/m² on days 1 and 8 of a 21 day cycle).

In order to be eligible for enrollment, patients had to meet the following criteria:

- Histologically or cytologically confirmed advanced or metastatic breast cancer
- Two to five prior cytotoxic chemotherapy regimens
- At least one cytotoxic chemotherapy regimen for advanced disease
- Progression on or within six months of the last prior chemotherapy regimen
- Measurable disease by independent radiological review.

The primary objective was to evaluate the objective response rate, defined as the number of patients with a best overall response of CR or PR, divided by the number of patients in the eligible population by independent radiographic review. The Eligible Population consisted of patients with measurable disease who received at least one dose of eribulin and met the above inclusion criteria.

The Calendar of Events is outlined below in Figure 2.

Figure 2: Calendar of Events for Study 211 (copied directly from the NDA submission)

Assessments	Screening	Treatment Cycle (Days)			Study Termination
	Days -28 to 0	Day 1	Day 8	Day 15 ^b	Within 30 days of final treatment
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Demographic Data	X				
Medical/Surgical History	X				
Tumor Assessments (RECIST) ^a	X			X	X
Confirmation of Diagnosis	X ^g				
ECOG Performance Status	X	X	X	X	X
Pain Assessment (VAS)		X	X	X	X
Physical Examination ⁱ	X	X	X	X	X
Vital Signs	X	X ^b	X ^b	X ^b	X ^b
12-Lead ECG (every other cycle)	X			X ^k	X
Pregnancy Test (if applicable)	X ^e	X ^e			
Hematology, Chemistry	X	X ^{c,d}	X ^{c,d}	X ^d	X
Urinalysis	X	X ^e			X
E7389 Administration		X	X		
PK Sampling ^f		X			
EORTC QOL Assessment ^j		X			X
Prior Medications and Procedures	X	X			
Concomitant Medications		X ^f	X ^f	X ^f	X
Adverse Events (AEs)		X ^f	X ^f	X ^f	X

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research on the Treatment of Cancer; PK = pharmacokinetic; QOL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; VAS = Visual Analog Scale

a – Radiologic scans of the chest, abdomen, and pelvis were performed at baseline. Radio-isotope bone scans were also performed at baseline (unless one had been performed within 6 weeks before enrollment). Post-baseline scans of the chest and abdomen were performed on a regular basis (every 2 cycles). Pelvic scans were not required after baseline if they were negative, unless clinically indicated. Post-baseline bone scans were performed only if clinically indicated. Study termination assessments included radiologic scans of chest and abdomen, (including pelvis only if involvement was indicated by previous scans), unless progression had been confirmed by radiologic measurements within the previous 28 days.

b – Vital signs recorded pre-dose on Days 1 and 8 for all cycles, post-dose on Day 1 of Cycle 1 only, and pre-dose on Day 15 for the first two cycles. Starting at Cycle 3, vital signs were collected predose only on Days 1 and 8, and otherwise only if clinically indicated.

c – Laboratory assessments were reviewed prior to drug administration. Assessments scheduled on Day 1 of Cycle 1 could be performed within 72 hours prior to the Day 1 visit of Cycle 1. Assessments scheduled on Day 1 of all other cycles, and on Day 8 and Day 15 of all cycles could be performed within 24 hours prior to scheduled visit.

d – Repeat complete blood count with differential and AE assessment at least every 3 days (until improvement to < Grade 3) if hematology assessment showed neutropenia or thrombocytopenia at any predose testing.

e – Urine or serum pregnancy test at screening and pre-dose on Day 1, Cycle 1 only.

f – Concomitant medications and AEs were collected post-dose on treatment days.

g – It was strongly encouraged that a counterstained, glass-covered slide or the fixed, paraffin-embedded sample of the patient's tumor from the diagnostic biopsy or surgical resection be obtained.

h - Day 15 (no dose scheduled) assessments were only performed for the first two cycles, unless clinically indicated

i - A complete physical examination was done at screening, Day 1 of every cycle, and at study termination. A symptom-directed physical examination was performed on Day 8 of every cycle and Day 15 of the first two cycles, and thereafter if applicable.

j - Every second cycle, before drug administration and before patients were informed of their tumor assessment

k - ECGs recorded at the end of Cycle 2 only.

Study 201

The original protocol for this study was issued on August 6, 2004. Study 201 is a phase 2, open-label, single arm study evaluating the safety and efficacy of eribulin in

104 patients with advanced metastatic breast cancer previously treated with anthracycline and taxane chemotherapy. Initially, 71 patients were enrolled to receive eribulin dosed at 1.4 mg/m² on Days 1, 8, and 15 of a 28-day cycle. However, because a substantial number of patients required dose interruptions, delays, reductions or omissions during the first two cycles of the 28-day regimen, an amendment to the protocol was submitted on July 1, 2005. This amendment added an additional cohort of 33 patients to receive eribulin on the same 21-day schedule used for Study 305 and Study 211 (1.4 mg/m² on Days 1 and 8 of a 21 day cycle).

In order to be eligible for enrollment, patients had to meet the following criteria:

- Histologically or cytologically confirmed advanced or metastatic breast cancer
- Prior treatment with an anthracycline and a taxane
- Progression on or within six months of the last prior chemotherapy regimen or progression while receiving chemotherapy for advanced/metastatic disease
- Measurable disease by RECIST.

The primary objective was to evaluate the overall response rate, defined as the number of patients with a best overall response of CR or PR confirmed 4 to 8 weeks after it was first observed. Tumor response and progression were evaluated using RECIST criteria. Blinded, independent review of radiographic images was performed for all patients except those who progressed on or before the Cycle 2 scan by investigator assessment. Secondary endpoints included duration of response, and estimation of progression-free survival and overall survival. The results of independent review were used for the primary analysis. The population used for the primary efficacy analysis consisted of the per-protocol population, defined as patients with measurable disease that had progressed within 6 months of their prior chemotherapy treatment and received at least one dose of eribulin.

The Calendar of Events for Study 201 is outlined below in Figure 3.

Figure 3: Calendar of Events for Study 201 (copied from NDA submission)

Table 1 Schedule of Assessments for the 28-Day Cycle

Assessments	Screening		Treatment Cycles (days)			Study Termination
	Days -14 to 0	Day 1	Day 8	Day 15	Day 22 ^f	+30 Days ^g
Informed Consents (study and pharmacogenomics)	X					
Inclusion/Exclusion Criteria	X ^h	X ^h				
Demographic Data	X					
Medical/Surgical History	X					
Physical Exam ^l	X	X	X	X	X	X
ECOG Performance Status	X	X				X
Vital Signs	X	X	X	X	X	X
Hematology	X	X ^{b,c}	X ^{b,c}	X ^{b,c}	X ^{b,c}	X ^{b,c}
Chemistry Labs	X	X ^b	X ^b	X ^b	X ^b	X ^b
Urinalysis	X	X ^b				X ^b
E7389 Administration		X	X	X		
FACT-B	X	X				X
Pain Visual Analog Scale (VAS)	X	X				X
Pregnancy Test	X	X ^d				
12-Lead ECG	X ^h	X ^h				X ^h
Prior Medications and Procedures	X	X				
Concomitant Medications		X ^f	X	X	X	X
Tumor Assessment (RECIST)	X ^e	X ^e				X
Adverse Events (AEs)	X	X ^f	X	X	X	X
Dispense Analgesics Diary	X	X				
Collect Analgesic Diary		X				X

AEs – adverse events; ECG – electrocardiogram; ECOG – Eastern Cooperative Oncology group; RECIST – Response Evaluation Criteria in Solid Tumors; FACT-B – Functional Assessment of Cancer Therapy-Breast; VAS – Visual Analog Scale

a Survival was assessed every 3 months. Any ongoing toxicities were assessed 30 days after the last dose of study drug and any unconfirmed CR or PR was confirmed.

b Assessments scheduled on Day 1 of Cycle 1 were performed within 72 hours prior to Day 1 visit. Assessments scheduled on Day 1 of all other cycles, Day 8 and Day 15 were performed within 24 hours prior to scheduled visit

c Repeat complete blood count with differential & severity assessment at least 3 days (until improvement to < Grade 3) if hematology assessment shows neutropenia or thrombocytopenia ≥ Grade 3 in Cycle 1, as per standard medical practice.

d Serum pregnancy test at screening and a urine or serum pregnancy test Day 1 pre-dose, Cycle 1 only.

e Baseline tumor assessment, consisting of radiologic evaluation of the chest and abdomen, was performed within 4 weeks prior to E7389 administration and then once every second cycle or sooner if there was evidence of disease progression

f Toxicity Assessment, Concomitant Medications and AEs were collected post-dose on Day 1

g Inclusion/Exclusion Criteria were done at screening and at pre-dose Day 1 Cycle 1 only

h ECG evaluations were performed at screening, pre-dose on Day 1 Cycle 1 only and at study termination

5.3.3 Additional Supportive Safety Studies

The following supportive studies evaluated eribulin in an additional 395 patients enrolled in studies of eribulin using dosing schedules different than that proposed for this NDA:

- Study 201: 70 patients who received eribulin in 28 day cycles
- Study 101: an open label, non-randomized dose-finding Phase 1 study in subjects with refractory advanced solid tumors. A total of 32 subjects received eribulin at doses of either 0.25 mg/m², 0.5 mg/m², 0.7 mg/m², 1.0 mg/m², or 1.4 mg/m² on Days 1,8, and 15 of a 28-day cycle.
- Study 102: an open-label single arm dose-finding Phase 1 study in 21 subjects with refractory advanced solid tumors. Patients were enrolled in dosing cohorts of 0.25, 0.5, 1, 2.8, and 4 mg/m².
- Study 103: an open-label, single arm, radiotracer mass-balance and treatment Phase 1 study in 6 subjects with refractory advanced solid tumors. Six subjects received 2 mg ¹⁴C-eribulin on Day 1 of the first cycle, and non-radiolabeled eribulin at a dose of 1.4 mg/m² for subsequent doses. Following completion of the first cycle, patients could enter an extension phase to continue eribulin therapy on Days 1 and 8 of a 21 day cycle.
- Study 108: an open-label, three-parallel group, Phase 1 PK study of eribulin in 17 patients with refractory advanced solid tumors with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment. All patients received an initial eribulin dose of 1.4 mg/m². Patients received either 1.4mg/m², 1.1 mg/m², or 0.7 mg/m² on Day 8 of the first cycle and subsequent cycles, depending on the degree of hepatic impairment.
- Studies 109: an open-label, randomized crossover PK and tolerability study of eribulin co-administered with multiple oral doses or ketoconazole in 12 patients with refractory advanced solid tumors. Eribulin doses ranged from 0.7-1.4 mg/m² on Days 1 and 8 of a 21-day cycle.
- Study 110: a single-arm, open-label, multicenter Phase 1 study evaluating the cardiac safety of eribulin in which 26 subjects with advance solid tumors received 1.4 mg/m² on Days 1 and 8 of a 21-day cycle.
- Study 202: a multi-center, open-label, single-arm Phase 2 study in patients with recurrent or advanced non-small cell lung cancer. 103 patients received either 1.4 mg/m² on Days 1, 8, and 15 of a 28-day cycle or 1.4 mg/m² on Days 1 and 8 of a 21-day cycle.
- Study 204: a multicenter, open-label two-stage design, single-arm Phase 2 study in which 108 subjects with hormone-refractory prostate cancer received 1.4 mg/m² on Days 1 and 8 of a 21-day cycle.

6 Review of Efficacy

Efficacy Summary

The primary assessment of eribulin efficacy is based on the endpoint of overall survival in Study 305, the only randomized trial submitted with this application. FDA analysis of Study 305 data confirms that a statistically significant prolongation in overall survival (OS) was observed in patients randomized to receive eribulin; median overall survival was 13.1 months in the eribulin arm (95% CI: 11.8, 14.3), compared to 10.6 months in the control arm (95% CI: 9.3, 12.5), with a hazard ratio of 0.809 (95% CI: 0.660 to 0.991; p-value: 0.041).

The European Medicines Agency (EMA) requested that Eisai provide an updated analysis of overall survival results after approximately 75% of patient deaths occurred. Analysis of this updated survival data, which reflects 589 deaths (77% of enrolled patients), confirms the results of the primary survival analysis. In the updated analysis, a 2.7 month improvement in OS was observed in the eribulin arm. The difference in OS was statistically significant, with a p-value of 0.014 based on a stratified log-rank test [HR: 0.81; 95% CI: (0.68, 0.96)].

Study 305's secondary efficacy parameters, progression-free survival and objective response rate, support the utility of eribulin in the setting of refractory metastatic breast cancer. Median progression-free survival was numerically prolonged by independent reviewer assessment but not statistically significant (potentially due to informative censoring); however, the difference in PFS was statistically significant by investigator assessment. Median progression-free survival by independent review was 45 days longer in the eribulin arm compared to the control arm [eribulin: 113 days (95% CI: 101,118), TPC arm: 68 days (95% CI: 63, 103); HR:0.865, (95% CI:0.714, 1.048; p = 0.137)]. Median progression-free survival by investigator review was 44 days longer in the eribulin arm compared to the TPC arm [eribulin: 110 days (95% CI: 100,114), control group: 66 days (95% CI: 60, 79); HR:0.757, (95% CI:0.638,0.900; p = 0.002)]. A superior response rate was observed in the eribulin arm which was statistically significant based upon independent review and investigator assessment. Based on independent reviewer assessment of the ITT population, the objective response rate was 11.2% (95% CI: 8.6% to 14.3%) for patients randomized to receive eribulin and 3.9% (95% CI: 1.9% to 7.1%) for patients in the TPC arm (p = 0.0006).

The applicant submitted supportive data from two single arm phase 2 studies in patients with locally advanced or metastatic breast cancer (studies E7389-A001-201 and E7389-G000-211) with primary endpoints of overall response rate that also demonstrated the activity of eribulin in the refractory setting. Overall response (all partial responses) based upon independent reviewer assessment was 11.5% (95% CI: 5.7% to 20.1%; median duration of response 171 days) and 9.3% (95% CI: 6.1% to 13.4%; median duration of response 126 days) in studies E7389-A001-201 and E7389-G000-211, respectively.

Results of subset analyses conducted by FDA and the applicant were generally consistent with those of the primary analysis. FDA statistical reviewers did not cite major statistical concerns with this application, concluding that the data submitted for Study 305 support achievement of its primary endpoint.

6.1 Indication

Eisai proposed the following indication for eribulin in the original NDA submission:

Halaven is a microtubule inhibitor indicated for the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane.

Comment:

(b) (4)

In addition, because Study 305 required patients to have been treated with a minimum of two prior regimens in the relapse or metastatic setting, this reviewer recommends adding this limitation to the indication.

6.1.1 Methods

This review will focus primarily on the efficacy results of the single randomized controlled trial, Study 305. A less in-depth analysis of efficacy data from two single-arm studies of eribulin in patients with refractory metastatic breast cancer (Study 201 and Study 211) is also included in this review. For details regarding the FDA statistical analysis of efficacy data submitted for this NDA, please refer to the statistical review conducted by Weishi Yuan.

Section 5.3.1 presents a summary of the study design and statistical analysis plan for Study 305. Briefly, Study 305 is an open label, randomized, multicenter, international study of eribulin in patients with refractory metastatic or locally recurrent breast cancer. In Study 305, 762 patients were randomized on a 2:1 basis to receive either eribulin (1.4 mg/m² intravenously on Days 1 and 8 of a 21-day cycle) or a single-agent therapy assigned by the investigator for each patient prior to randomization. Patients were stratified by HER2 status, prior capecitabine exposure, and geographical region. To qualify for enrollment, patient must have received two to five prior chemotherapy regimens, including an anthracycline and a taxane. In addition, enrolled patients experienced disease progression within six months of their most recent chemotherapy regimen and received a minimum of two prior chemotherapy regimens in the metastatic setting. The primary endpoint was overall survival (OS), with secondary endpoints of progression-free survival (PFS) and objective response rate (ORR). The primary analysis was pre-specified to occur after 411 patients died (representing 54% of the total number of enrolled patients).

6.1.2 Demographics

Study 305

Table 14 shows the baseline demographics and disease characteristics of subjects enrolled in Study 305. Baseline demographic and disease characteristics were generally well balanced between the two treatment arms. All enrolled patients were female, 92% were White, and 76% were post-menopausal. The majority of patients were enrolled in North America, Western Europe, or Australia; 19% of patients were enrolled in U.S. sites. The median age of patients at enrollment was 55 years. *Comment: In the United States, the median age of patients at diagnosis is 61 (SEER statistics). The patients in Study 305 tended to be younger, with a median age of 55 at enrollment.*

All but two patients had metastatic disease at enrollment. Sixteen percent of patients were HER2 positive, and HER2 status was unknown for 10% of patients. *The percentage of HER2 positive patients with unknown status is higher than would be expected in the United States, but is low enough to be acceptable to this reviewer.*

Table 14: Baseline Demographic and Disease Characteristics of Patients Enrolled in Study 305

Patient Characteristics	Eribulin N = (508)	TPC (N =254)	Total (N=762)
Age (years)			
Mean (sd)	55 (10)	56(10)	55 (10)
Median (range)	55 (28 - 85)	56 (27 - 81)	55 (27 – 85)
<40 (%)	34 (7)	17 (7)	51 (7)
40-<65 (%)	380 (75)	180 (71)	560 (74)
>= 65 (%)	94 (19)	57 (22)	151 (20)
Race (n, %)			
White	470 (93)	233 (92)	703 (92)
Black	20 (4)	14 (6)	34 (5)
Asian/Pacific Islander	3 (1)	2 (1)	5 (1)
Other	15 (3)	5 (2)	20 (3)
Geographic Region n (%)			
N. America/W. Europe/Australia	325 (64)	163 (64)	488 (64)
Eastern Europe	129 (25)	64 (25)	193 (25)
Latin America/South Africa	54 (11)	27 (11)	81 (11)
ECOG Performance status, n (%)			
0	217 (43)	103 (41)	320 (42)
1	244 (48)	126 (50)	370 (49)
2	39 (8)	22 (9)	61 (8)
Not reported	8 (2)	3 (1)	11 (1)
Reproductive Status			
Fertile	46 (9)	20 (8)	66 (9)

Patient Characteristics	Eribulin N = (508)	TPC (N =254)	Total (N=762)
Infertile	5 (1)	0 (0)	5 (1)
Surgically sterile	78 (15)	35 (14)	113 (15)
Post-menopausal	379 (75)	199 (78)	578 (76)
Estrogen receptor status, n (%)			
Positive	336 (66)	171 (67)	507 (67)
Negative	143 (28.1)	72 (28.3)	215 (28)
Unknown/not done	29 (6)	11 (4)	40 (5)
Progesterone receptor status, n (%)			
Positive	254 (50)	123 (48)	377 (49)
Negative	197 (39)	102 (40)	299 (39)
Unknown/not done	57 (11)	29 (11)	86 (11)
HER2 receptor status, n (%)			
Positive	83 (16)	40 (16)	123 (16)
Negative	373 (73)	192 (76)	565 (74)
Unknown	52 (10)	22 (9)	74 (10)
ER⁺, PR⁺, HER2⁺, n (%)	93 (18)	51 (20)	144 (19)
Time from original diagnosis (years)			
0 - < 2 n (%)	51 (10)	33 (13)	84 (11)
2 - < 10 n (%)	356 (70)	170 (67)	526 (69)
10 or more n (%)	101 (20)	51 (20)	152 (20)
Mean (sd)	7 (5)	7 (5)	7 (5)
Median (range)	5 (0 - 37)	5 (1 - 23)	5 (0 - 37)
Visceral Disease at Enrollment			
Present	413 (81)	211 (84)	624 (82)
Absent	90 (18)	40 (16)	130 (17)
Unknown	5 (1)	3 (1)	8 (1)
Number of Organs Involved			
1	85 (17)	35 (14)	120 (16)
2	172 (34)	82 (32)	254 (33)
3	145 (29)	77 (30)	222 (29)
4	71 (14)	37 (15)	108 (14)
5	24 (5)	16 (6)	40 (5)
≥6	9 (2)	7 (3)	16 (2)

Table 15 illustrates that the study population in Study 305 was heavily pre-treated. Enrolled patients received a median of 4 prior chemotherapy regimens, and virtually all had received prior anthracycline and taxane chemotherapy. Seventy-three percent of patients had received capecitabine therapy prior to enrollment. Eighty-three percent of HER2⁺ patients had received trastuzumab or lapatinib prior to enrollment. *Comment: HER2+ patients were not required to have received trastuzumab or lapatinib therapy prior to enrollment in Study 305. It is standard of care in the United States for patients with breast cancer that overexpresses HER2 to receive trastuzumab or lapatinib; however, in this reviewer's opinion, 83% receiving anti-HER2 therapy was sufficiently high enough for*

meaningful extrapolation of the results of Study 305 to patients with HER2⁺ breast cancer in the United States.

Table 15: Prior Anti-Cancer Therapy – Study 305

Parameter	Eribulin N = (508)	TPC (N =254)	Total (N=762)
Number of Previous Chemotherapy Regimens n (%)			
≤ 3	242 (48)	114 (45)	356 (47)
> 3	264 (52)	139 (55)	403 (53)
Number of Previous Chemotherapy Regimens for Metastatic Disease n (%)			
≤ 3	391 (77)	180 (71)	571 (75)
> 3	117 (23)	73 (29)	190 (25)
Number of patients who previously received; n(%)			
Taxanes	503 (99)	251 (99)	754 (99)
Anthracyclines	502 (99)	250 (98)	752 (99)
Capecitabine	370 (73)	189 (74)	559 (73)
Number of patients refractory to: n (%)^a			
Taxanes	410 (81)	204(80)	614 (81)
Anthracyclines	284 (56)	156 (61)	440 (58)
Capecitabine	342 (67)	174 (69)	516 (68)
HER2⁺ patients previously received Trastuzumab or Lapatinib n (%)^b	67 (81)	35 (88)	102 (83)
Duration of last chemotherapy (months)^c			
Median (range)	3.6 (0,32)	3.5 (0,25)	3.5 (0,32)
Prior radiotherapy n (%)			
Yes	420 (83)	195 (77)	615 (81)
No	88 (17)	59 (23)	147 (19)

^{a.} refractory was defined as progression within six months of receipt of chemotherapy

^{b.} percentage based upon the total number of patients with HER2 positive status

Study Population

^{c.} patients whose last chemotherapy had duration of zero received a single dose of that chemotherapy prior to study enrollment.

Table 16 illustrates that the two groups were comparable with respect to the previous chemotherapy regimens received in the metastatic or locally advanced setting. The median duration of the last chemotherapy for metastatic disease prior to study entrance was 3.6 months in the eribulin arm and 3.5 months in the TPC arm.

Table 16: Prior Chemotherapies for Advanced Disease

Chemotherapy	Eribulin N = 508		TPC N = 254	
	n	%	n	%
Capecitabine	364	72	182	72
Paclitaxel	267	53	112	44
Docetaxel	264	52	143	56
Vinorelbine	201	40	95	37
Cyclophosphamide	188	37	111	44
Doxorubicin	183	36	102	40
Fluorouracil	147	29	81	32
Gemcitabine	131	26	65	26
Letrozole	109	21	66	26
Exemestane	99	19	51	20
Anastrozole	95	19	48	19
Epirubicin	91	18	56	22
Fulvestrant	84	17	44	17
Trastuzumab	78	15	38	15
Tamoxifen	74	15	53	21
Bevacizumab	59	12	36	14
Carboplatin	57	11	34	13
Investigational drug	35	7	12	5
Cisplatin	27	5	30	12
Goserelin	25	5	10	4
Methotrexate	25	5	18	7
Lapatinib	20	4	13	5

6.1.3 Subject Disposition

A total of 762 patients were randomized to the two study arms; 508 patients were randomized to the eribulin arm and 254 were randomized to the TPC arm. As of May 12, 2009, 484 of the 508 patients (95.3%) randomized to the eribulin arm discontinued study treatment, compared to 244 of 254 TPC patients (96.1%). Section 7.3.3 of this review contains a discussion of the reasons for patient withdrawal from study treatment, including deaths and adverse events. The majority of patients in both arms discontinued due to disease progression. A higher percentage of patients in the eribulin arm discontinued therapy due to progressive disease (eribulin: 66% versus TPC: 61%); however, a higher percentage of patients discontinued study therapy due to clinical progression in the TPC arm (TPC: 14% versus eribulin: 12%). The percentages of patients who discontinued study therapy due to death or adverse events were similar in the two arms (see Table 51 for details).

TPC Therapy

Patients in the TPC arm were treated with single agent chemotherapy, hormonal therapy or biological therapy that was chosen and recorded by their physician prior to randomization. The protocol included best supportive care as a TPC treatment option; however, no TPC patients received supportive care therapy while enrolled in Study 305. Table 17 provides a summary of therapies assigned and received by patients enrolled in Study 305. Most patients randomized to the TPC arm received chemotherapy, which was planned for 246 (96.9%) patients and actually received by 238 (93.7%) patients. Vinorelbine was the most common chemotherapy administered to TPC patients, followed by gemcitabine and capecitabine. A minority of patients received hormonal therapy. *Comment: the treatments assigned to TPC patients appear reasonable.*

Table 17: Categories of Therapy Received by Patients Enrolled in Study 305
 (copied from FDA statistical review)

Treatment	Assigned n (%)	Actual n (%)
Eribulin	508 (100.0)	503 (99.0)
TPC: Vinorelbine	65 (25.6)	61 (24.0)
TPC: Gemcitabine	46 (18.1)	46 (18.1)
TPC: Capecitabine	45 (17.8)	44 (17.3)
TPC: Taxanes	41 (16.1)	38 (16.1)
TPC: Anthracyclines	24 (9.4)	24 (9.4)
TPC: Hormone therapy	8 (3.1)	9 (3.5)
TPC: Others	25 (9.8)	25 (9.8)

6.1.4 Analysis of Primary Endpoint(s)

Reviewer's comments; All efficacy analyses presented in the following sections were conducted in collaboration with the Division of Biometrics, Biologics and Therapeutics Statistical Staff, Weishi Yuan, Mathematical Statistician. All statistical analyses were conducted by Ms. Yuan. Please refer to her review for additional details regarding the statistical analyses.

The primary efficacy endpoint for Study 305 is overall survival (OS), defined as the time randomization until death from any cause. Patients who were lost to follow-up were censored at the date they were last known to be alive. Patients who were alive on the data cut-off date (May 12, 2009) were censored at the cut-off date for OS analyses.

Twenty-five percent of the case report forms (CRFs) submitted by the applicant were audited during the clinical review to verify that the survival data contained in the datasets

were an accurate reflection of the patient information documented in the CRFs. No discrepancies between the CRFs and datasets were observed.

The statistical analysis plan specified that the final analysis of overall survival would occur after 411 deaths occurred. In addition, the statistical analysis plan included a planned interim analysis when half of the events (206 deaths) had been observed; based upon this interim analysis, the study could be stopped early for OS superiority or lack of efficacy. The nominal significance level to stop Study 305 for superior efficacy at the interim analysis was 0.003 and the nominal significance level of the final analysis was 0.049.

As specified in the statistical analysis plan, the Data Monitoring Committee conducted an interim analysis of OS based upon a August 23, 2008 cut-off date, when 207 deaths had been reported. The DMC noted a statistically significant treatment effect ($p = 0.0018$) using the Cox model, which was deemed a more appropriate method to evaluate the treatment effect because some randomization strata had small numbers of patients. However, the DMC unanimously concluded that Study 305 should proceed until the 411 deaths occurred. DMC meeting minutes indicate that the Committee was particularly concerned about the robustness of the interim data due to an “apparent evolving difference in treatment effect on survival between the August 23, 2008 data and more recent IVRS data.” At the time of data cut-off for the scheduled interim analysis on August 23, 2008, 29% of patients in the eribulin arm had died, compared to 36% of patients on the TPC arm. However, by January 2009, 32.6% of patients in the eribulin treatment arm had died compared to 36.4% of TPC patients.

The final analysis of OS used a two-sided stratified log-rank test with a type 1 error rate of 0.049. The test was stratified by HER2/*neu* status, prior capecitabine exposure, and geographical region. The hazard ratio (HR) for OS was estimated using a Cox regression model, which was also adjusted for HER/*neu* status, prior capecitabine exposure, and geographical region. At the time of the pre-specified OS analysis, survival status for the majority of patients was known; six patients who were lost to follow-up were censored at the time they were last known to be alive (0.8% of patients in each treatment arm).

Table 18 summarizes the results of the FDA statistical analysis of overall survival data submitted by the applicant for the Intent-to-Treat (ITT) population after 422 deaths were observed. There was a statistically significant prolongation of overall survival (p -value = 0.041; HR = 0.81, 95% CI: 0.66 to 0.99). The median OS of patients randomized to receive eribulin was 2.5 months longer than the median OS of patient randomized to the TPC arm.

Table 18: Overall Survival Analysis Using the ITT Population of Study 305 (adapted from FDA statistical review)

Overall Survival	Eribulin (n=508)	TPC (n=254)
Number of deaths (%)	274 (54)	148 (58)
Median, months (95% CI)	13.1 (11.8, 14.3)	10.6 (9.3, 12.5)
Hazard Ratio (95% CI) ^a	0.81 (0.66, 0.99)	
p-value ^b	0.041	

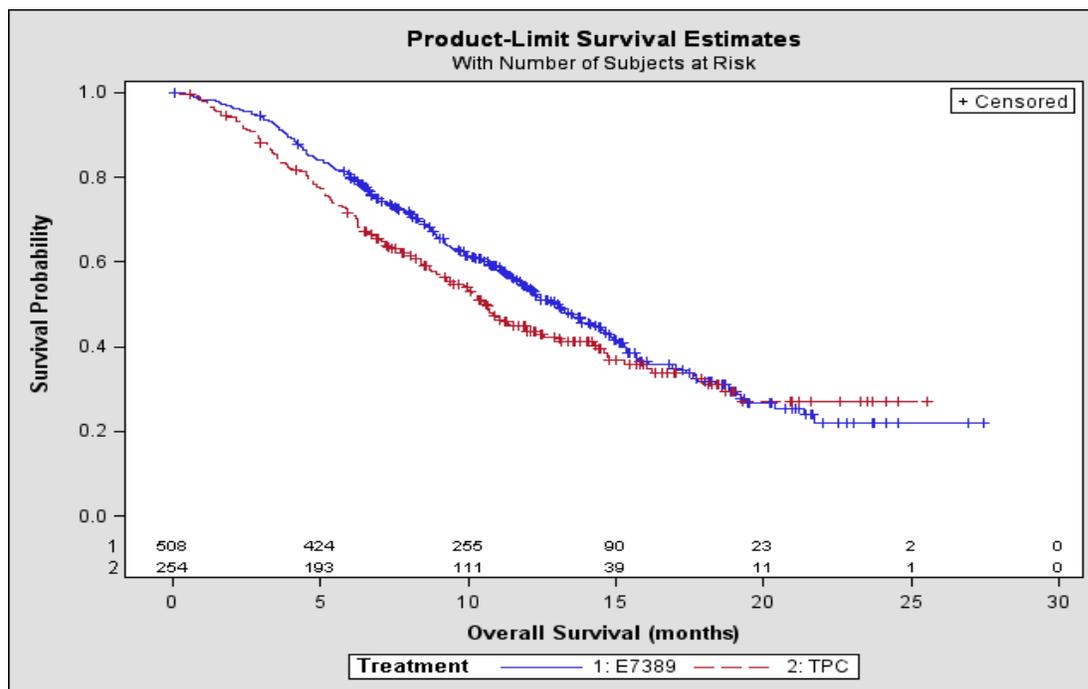
Abbreviations: CI, confidence interval

^a Based on a Cox proportional hazards model stratified by geographic region, HER2 status, and prior capecitabine therapy.

^b Based on a log-rank test stratified by geographic region, HER2 status, and prior capecitabine therapy.

Figure 4 shows the estimated Kaplan-Meier curve for the distribution of OS in Study 305. Based upon the Kaplan Meier Analysis, the improvement in OS in the eribulin arm was apparent within 2 months of therapy, and this benefit was maintained until about 15 months had elapsed from the initiation of treatment.

Figure 4: Kaplan-Meier Curve for the Distribution of Overall Survival for Study 305 (copied from FDA statistical review)



Comment: The curves appear to cross at about 20 months. However, conclusions based on this observation should be considered tenuous because of the small number of patients at risk at the point when the curves cross. Additionally, the curves do not cross in the updated survival analysis.

The OS analysis submitted by the applicant was based upon of data reflecting 422 deaths, but the analysis was pre-specified to occur after 411 enrolled patients died. The FDA statistical reviewer conducted a sensitivity analysis for OS after 411 deaths occurred, and confirmed that the results remained statistically significant (p-value = 0.040; HR = 0.807, 95% CI: 0.66, 0.99).

Table 19 shows the results of an additional sensitivity analysis of OS using the per-protocol (PP) population, conducted by the FDA statistical reviewer and applicant. The PP population excluded 49 patients in the eribulin arm and 28 in the TPC arm who had certain specified protocol violations. Although the HR and median for OS in the PP population were similar to those of the ITT population; the results were not statistically significant.

Table 19: Overall Survival Analysis Using Per-Protocol Population - Study 305
 (adapted from FDA statistical review)

Overall Survival – PP Population	Eribulin N = 459	TPC N = 216
Number of Deaths (%)	244 (53.2%)	123 (56.9%)
Median Survival, months (95% CI)	13.1 (11.8, 14.3)	10.6 (9.3, 12.5)
p-value	0.066	
HR	0.81 (0.65, 1.02)	

Comment: the lack of statistical significance in the PP population may be due to the smaller number of patients included in the analysis.

OS Analysis Based Upon Updated Survival Data

During the course of clinical development of eribulin, the European Medicines Agency (EMA) requested that updated survival information from Study 305 reflecting a greater level of data maturity than that of the preplanned analysis be included in the regulatory submission. A target level of 75% of deaths was chosen for the updated OS analysis. In compliance with FDA's request, Eisai submitted this updated survival data on July 28, 2010 with the 120-day safety update.

Seventy-five percent of patient deaths (576/762) were observed on March 2, 2010. Patients who remained on study were then followed up to document survival status. Patients who were lost to follow-up were censored at the last known date alive, and

patients who were successfully contacted and documented to be alive were censored on March 3, 2010. Following this data sweep, the updated survival analysis reflected 589 events (77.3% of enrolled patients).

Table 20 shows the survival status of patients in the updated OS analysis. At the time of the updated analysis, 113 of 508 patients (22%) in the eribulin arm and 46 of 254 (18%) patients in the TPC arm remained alive. Fourteen patients who withdrew consent for follow-up or who were not successfully contacted were censored prior to the March 3, 2010 cut-off date; the distribution of these patients was similar in the treatment arms.

Table 20: Patient Survival Status at the Time of Data-Cut-Off for Updated OS Analysis for Study 305 (adapted from clinical study report)

Survival Status at Data Cut-Off	Eribulin N = 508 n (%)	TPC N = 254 n (%)	Total N = 762 n (%)
Alive	113 (22)	46 (18)	159 (21)
Dead	386 (76)	203 (80)	589 (77)
Lost to follow-up or Consent withdrawn	9 (2)	5 (2)	14 (2)

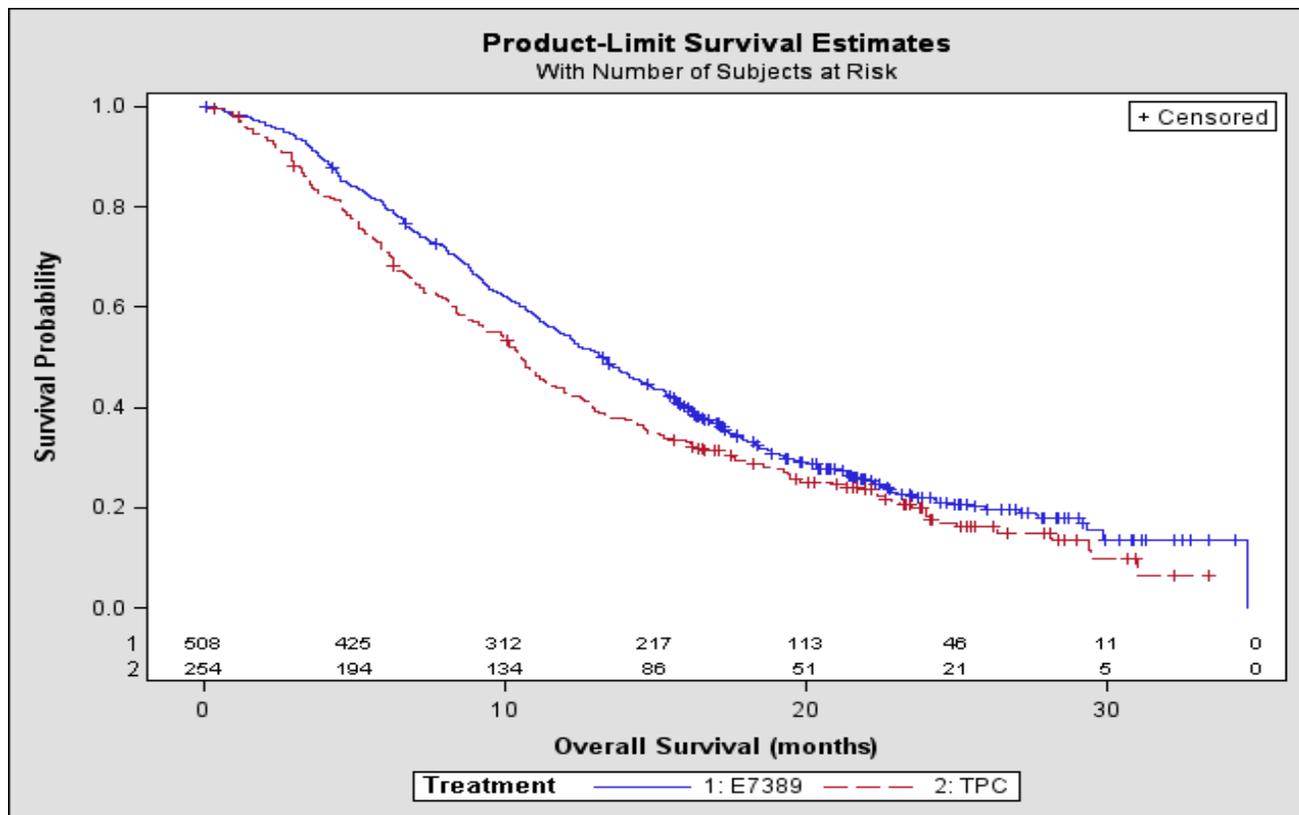
Table 21 illustrates that the updated OS analysis was consistent with the primary analysis. Patients in the eribulin arm experienced a 2.7 month improvement in median OS compared to patients in the TPC arm (p = 0.014; HR = 0.81, 95% CI: 0.68 to 0.96).

Table 21: Results of Overall Survival Analysis Based Upon Updated Data in the ITT Population (adapted from FDA statistical review)

Overall Survival	Eribulin N = 508	TPC N = 254
Number of Deaths (%)	386 (76.0%)	203 (79.9%)
Median Survival – months (95% CI)	13.2 (12.1, 14.3)	10.5 (9.2, 12.0)
p value	0.014	
HR	0.81 (0.68, 0.96)	

Figure 5 shows the Kaplan-Meier curve for the distribution of OS based upon the updated survival data. This curve illustrates that the survival benefit continues to be maintained throughout most of the study period.

Figure 5: Kaplan-Meier Curve for the Distribution of Overall Survival Using Updated Survival Data for Study 305 (copied from FDA statistical review)



In this reviewer's opinion, the results of this post-hoc OS analysis (requested by EMEA), reflecting more mature data than the primary analysis, strengthen this application.

The applicant provided an analysis of OS in the per-protocol (PP) population using the updated survival data. This analysis indicated that the OS results for the PP population (p-value = 0.009; HR = 0.778, 95% CI = 0.645 to 0.939) were consistent with the results in the ITT analysis.

6.1.5 Analysis of Secondary Endpoints(s)

PFS, defined as the time from randomization until disease progression or death due to any cause, was a secondary endpoint for Study 305. PFS was assessed using RECIST criteria by independent review of imaging data by (b) (4). Objective tumor response rate (ORR), using RECIST criteria in patients with measurable disease, and duration of response were also secondary endpoints.

Progression-Free Survival (PFS)

Table 22 shows the results of the PFS analysis of the ITT population based upon independent review, and Figure 6 shows the Kaplan-Meier curve for the distribution of PFS. PFS in the eribulin arm was numerically longer compared to the TPC group, but the results did not reach the level of statistical significance.

Table 22: Progression Free Survival Based upon Independent Review for Study 305
 (adapted from FDA statistical review)

Parameter	Eribulin N = 508	TPC N = 254
Number of Events (%)	357 (70.3)	164 (64.6)
Median PFS, months (95% CI)	3.7 (3.3, 3.8)	2.2 (2.1, 3.4)
p-value	0.137	
HR	0.87 (0.71, 1.05)	

Figure 6: Kaplan--Meier Curve for the Distribution of Progression-Free Survival by Independent Review for Study 305 (copied from FDA statistical review)

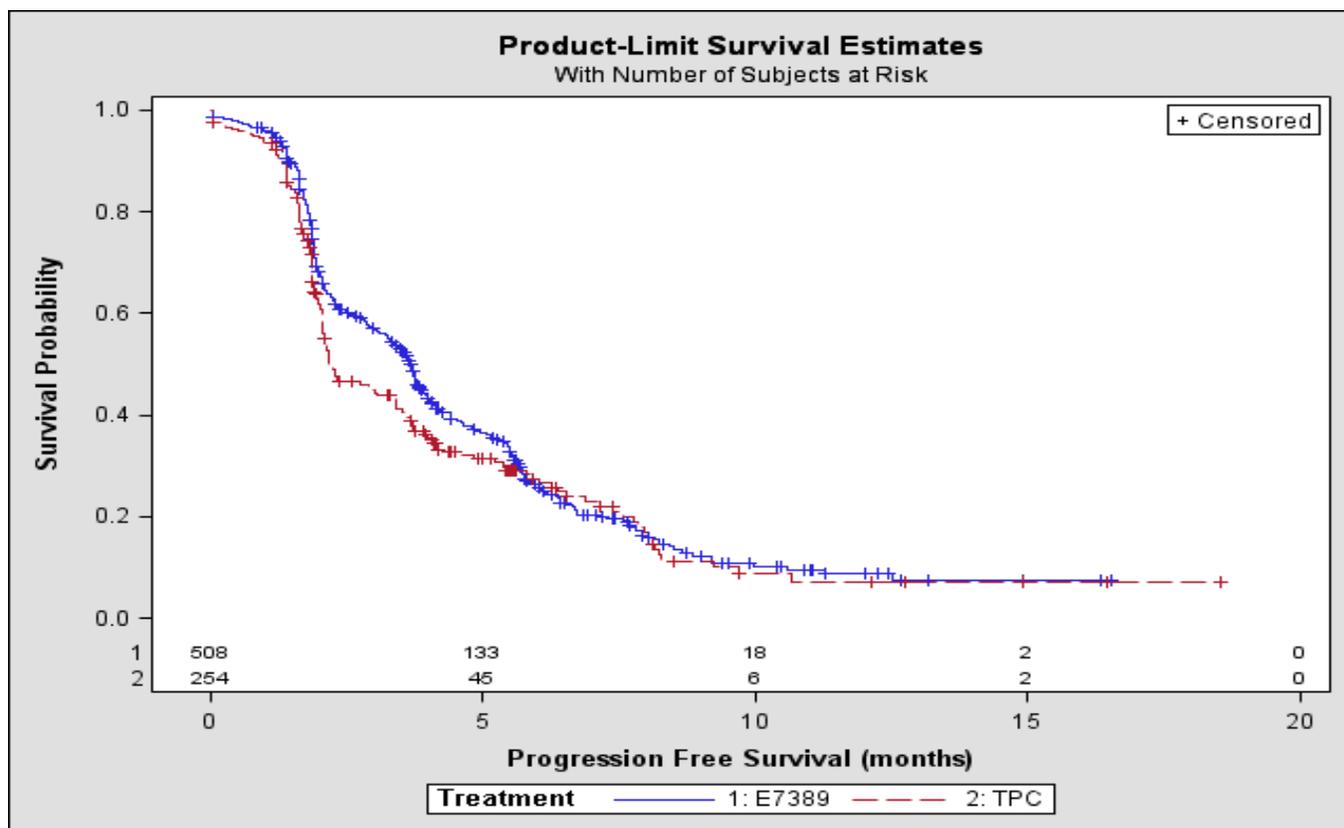


Table 23 shows a comparison of the PFS analyses based upon independent review and investigator assessment conducted by the applicant. Median PFS values based upon investigator assessment of PFS were similar to those derived from independent review; however, the results were (nominally) statistically significant. ($p = 0.002$; HR = 0.76, 95% CI: 0.638 to 0.900).

Table 23: Applicant's Analysis of PFS by Independent and Investigator Review (ITT Population) - Study 305 (adapted from clinical study report)

Parameter	Independent Review		Investigator Review	
	Eribulin N = 508	TPC N = 254	Eribulin N = 508	TPC N = 254
Number of Patients Censored (%)	151 (29.7)	90 (35.4)	79 (15.6)	48 (18.9)
Number of Events (%)	357 (70.3%)	164 (64.6%)	429 (84.4)	206 (81.1)
Median PFS - days (95% CI)	113 (101, 118)	68 (63, 103)	110 (100, 114)	66 (60, 79)
p-value	0.137		0.002	
HR	0.87 (0.71, 1.05)		0.76 (0.64, 0.90)	

Fewer patients were censored in the analysis of PFS based upon investigator assessment compared to the PFS analysis based upon independent review for several reasons. First, patients whom the investigators diagnosed with progressive disease based upon RECIST did not have follow-up scans and were therefore censored if independent reviewers disagreed with the investigator assessment. In addition, patients with non-measurable disease were censored if they experienced disease progression without radiographic progression of non-target lesions or appearance of new lesions. Finally, patients who discontinued due to clinical progression were censored in the PFS analysis by independent review.

Objective Response Rate (ORR)

Objective response rate (ORR) was measured using RECIST criteria in patients with measurable disease. Table 24 presents the FDA statistical analysis of ORR based upon independent reviewer assessment of the ITT population. Based on independent review, the ORR was 11.2% (95% CI = 8.6%, 14.3%) for patients in the eribulin arm and 3.9% (95% CI = 1.9%, 7.1%) for patients in the TPC group, with a nominal p-value of 0.0006. Most of the responses were partial responses.

The three complete responses were documented by temporary disappearance of lymph nodes:

- Disappearance of a 23 mm right axillary lymph node for 145 days was documented for patient 16041011,

- Disappearance of a 9 mm axillary lymph node for 305 days was documented for patient 19041003, and
- Disappearance of a retroperitoneal lymph node for 58 days was documented in patient 20081041.

Table 24: Objective Response Rate Based Upon Independent Review – Study 305
 (adapted from FDA statistical review)

Parameter	Eribulin n=508 (%)	TPC n=254 (%)	p-value
Objective Response Rate (CR+PR)	57 (11.2)	10 (3.9)	0.0006
Complete Response (CR)	3 (0.6)	0 (0)	
Partial Response (PR)	54 (10.6)	10 (3.9)	
Stable Disease (SD)	208 (40.9)	96 (37.8)	
Progressive Disease (PD)	190 (37.4)	105 (41.3)	
Non Evaluable (NE)	47 (9.3)	40 (15.8)	
Unknown (UN)	6 (1.2)	3 (1.2)	

Comment: In this reviewer's opinion, the response rate achieved by patients in the eribulin arm is acceptable in this highly-refractory population, especially in light of the demonstrated improvement in overall survival.

Duration of Response

Thirty-one of the 57 patients who exhibited responses to eribulin therapy progressed before the data cut-off date. The median duration of response was 4.2 months (95% CI: 3.8 to 5.0). The median duration of response was longer for the 10 patients who responded to TPC therapy (6.7 months, with 95% CI: 3.4 to 7.0).

6.1.6 Other Endpoints

There were no additional efficacy endpoints considered for regulatory decision making from Study 305 other than OS, PFS, ORR, and duration of response.

6.1.7 Subpopulations

Gender

All patients enrolled in Study 305 were women. Therefore, subgroup analyses for gender were not conducted.

Age

Table 25 presents the results of the FDA statistical analysis of OS by Age. Based upon this subgroup analysis, the overall survival benefit conferred by eribulin appears to be lower in elderly patients. However, this subgroup analysis should be interpreted with caution due to the small number of patients that comprised this age group in Study 305.

Table 25: Subgroup Analysis of Overall Survival by Age- Study 305 (adapted from FDA statistical review)

Subgroups	Eribulin	TPC
Age < 65		
N	414	197
Number of Deaths (%)	222 (53.6)	120 (60.9)
Median Survival, months (95% CI)	13.0 (11.6, 14.6)	10.3 (8.7, 12.0)
HR	0.79 (0.64, 0.99)	
Age ≥ 65		
N	94	57
Number of Deaths (%)	52 (55.3)	28 (49.1)
Median Survival, months (95% CI)	13.1 (10.8, 15.3)	11.4 (8.2, NE)
HR	0.96 (0.61, 1.53)	

Table 26 presents the results of the FDA statistical analysis comparing OS for Caucasians with Non-Caucasians. Based upon this subgroup analysis, the overall survival benefit conferred by eribulin appears more pronounced in Caucasians. However, this subgroup analysis should be interpreted with caution due to the small number of non-White patients enrolled in Study 305.

Table 26: Subgroup Analysis of Overall Survival by Race - Study 305 (adapted from FDA statistical review)

Subgroups	Eribulin	TPC
Caucasians		
N	470	233
Number of Deaths	249 (53.0)	136 (58.4)
Median Survival, months (95% CI)	13.1 (12.0, 14.6)	10.7 (9.3, 12.5)
HR	0.80 (0.65, 0.99)	
Non-Caucasians		
N	38	21
Number of Deaths	21 (55.3)	12 (57.1)
Median Survival	9.5 (5.7, 14.4)	8.9 (5.7, NE)
HR	1.19 (0.60, 2.37)	

Other Special/Subgroup Populations

The clinical study report included several additional subgroup analyses for OS, which were verified by FDA statistician, Weishi Yuan. Forest plots illustrating the results of pertinent analyses are shown in Figure 7.

Figure 7: Subgroup Analyses Conducted by Applicant for Study 305 (copied from the Applicant’s clinical study report)

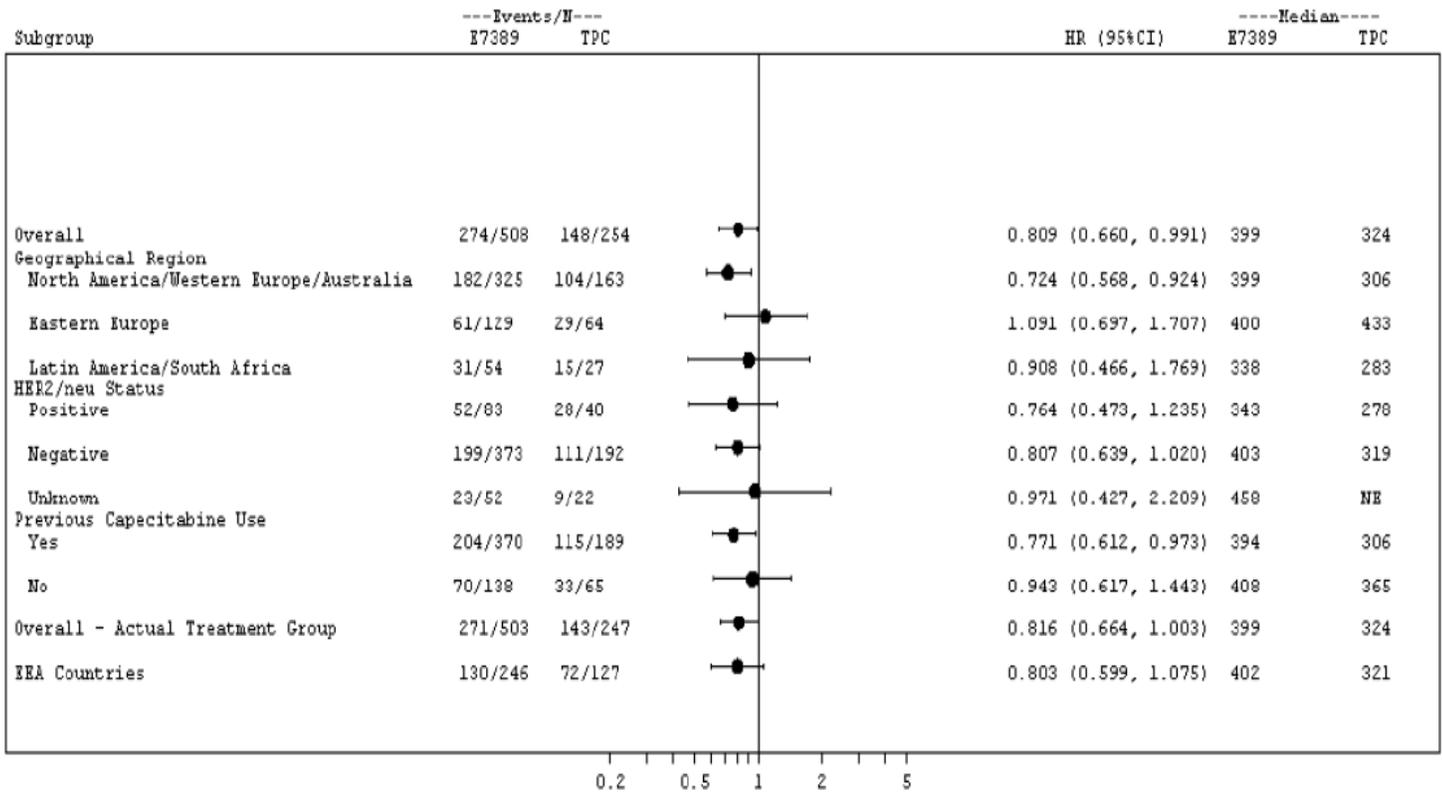


Figure 7 (continued)

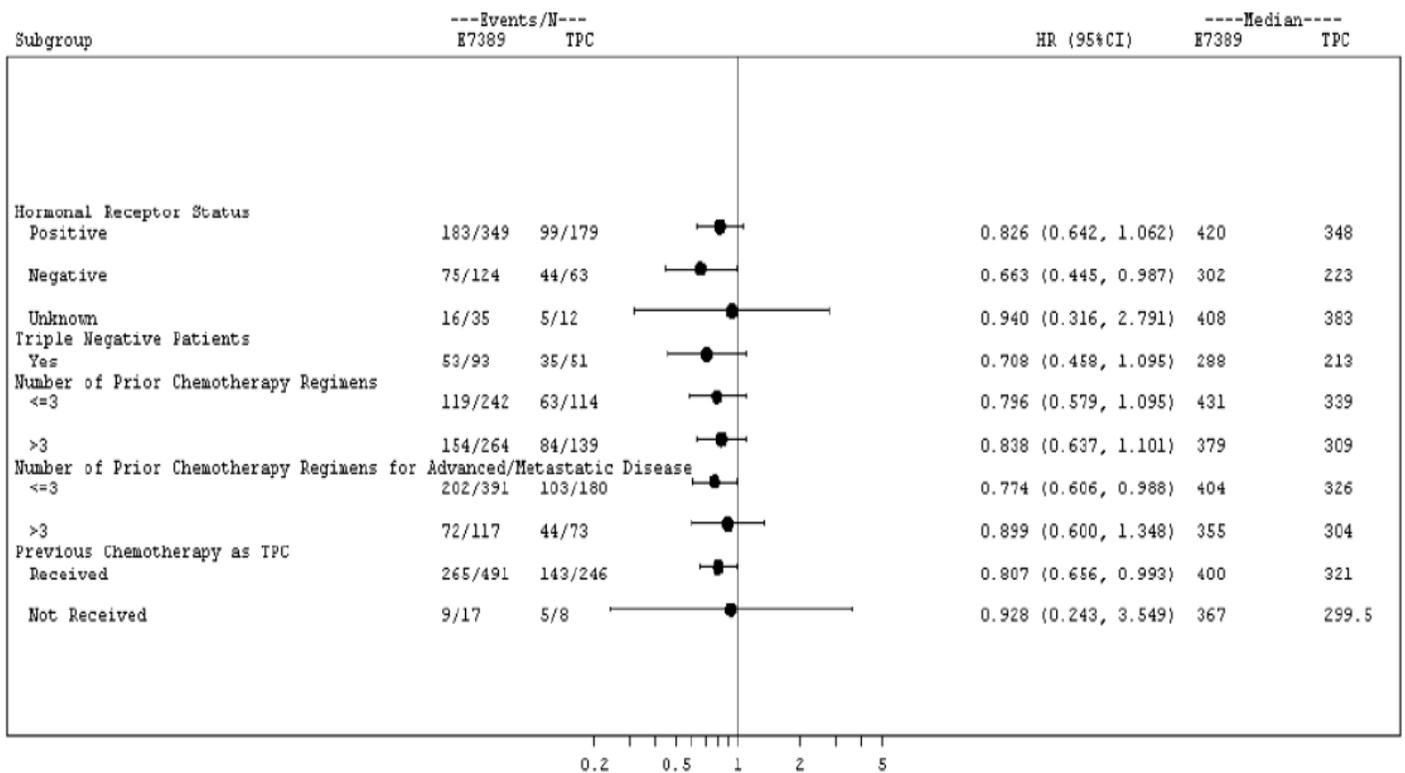
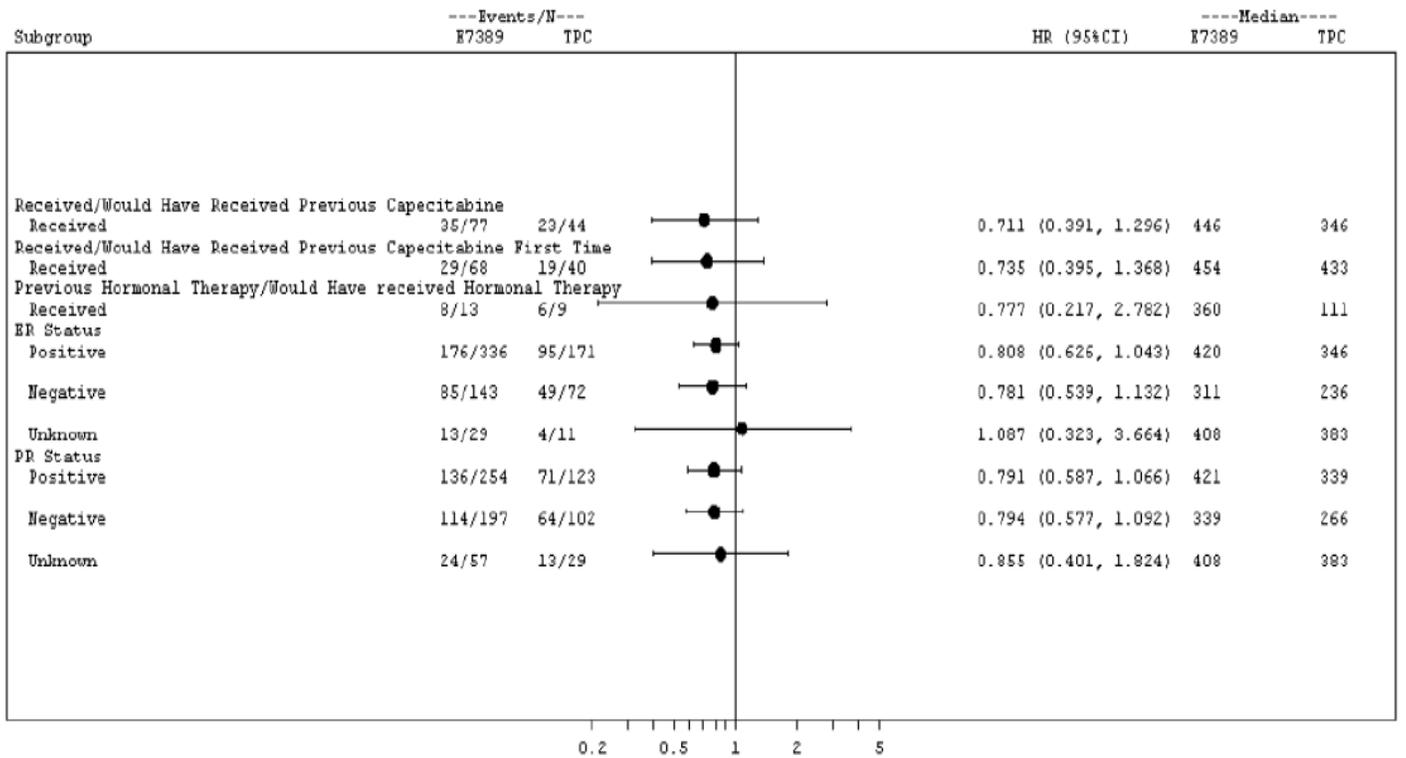


Figure 7 (continued)

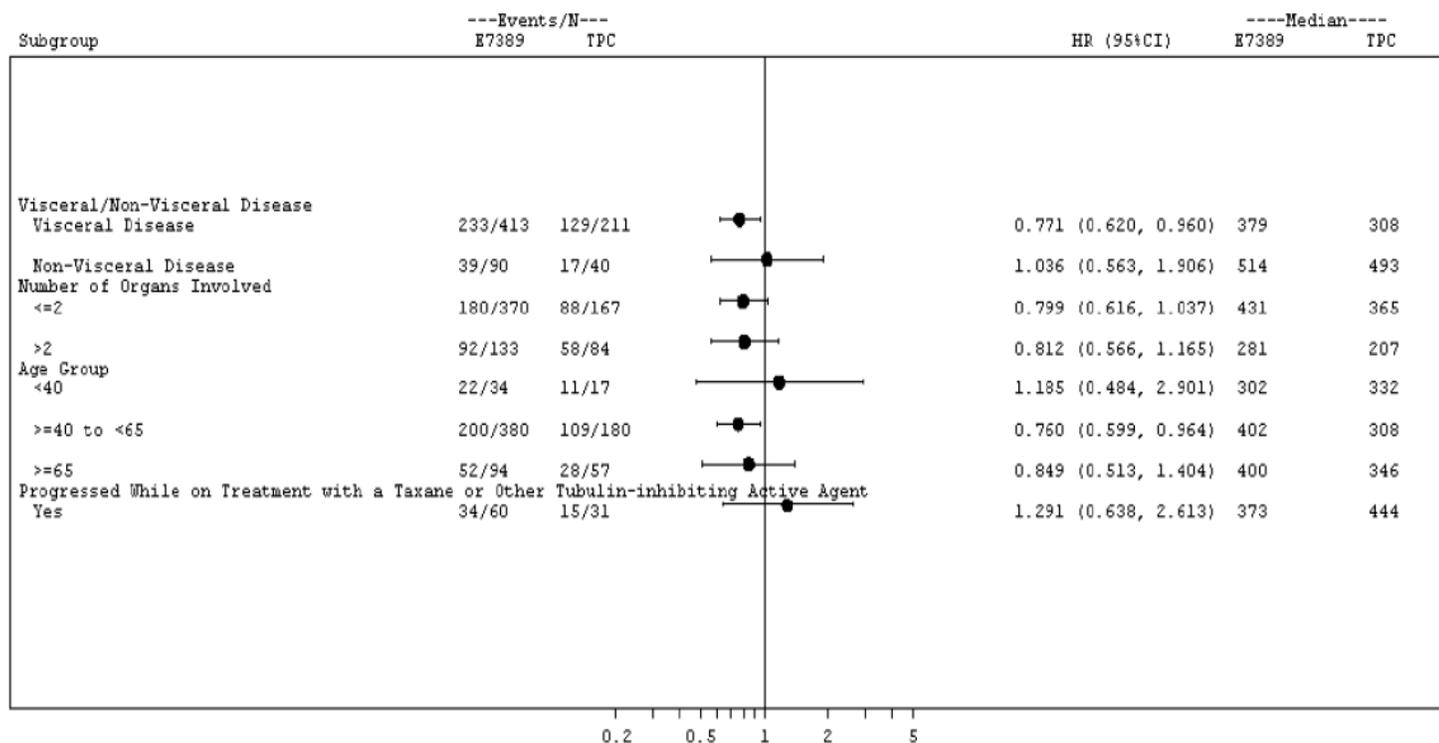


Table 27 shows the results of subgroup analyses conducted by FDA. The results of the subgroup analyses were generally consistent with the primary analysis of OS in the ITT population. The subgroup analysis by regional strata displayed a trend toward a more pronounced improvement in OS in patients randomized to the eribulin arm in N. America, W. Europe, and Australia (HR = 0.73, 95% CI = 0.57 to 0.92.) compared to patients enrolled in other regions. Patients randomized to the eribulin arm in the United States exhibited a less pronounced trend toward improved overall survival; however, the relatively small sample size makes interpretation of these results difficult.

The subgroup of patients with prior capecitabine exposure (HR = 0.77; 95% CI = 0.61 to 0.97) appeared to have improved OS compared to patients who had not received prior capecitabine therapy. Subgroup analyses also demonstrated a trend toward improved OS in patients with tumors with HER2 overexpression or triple negative status. Subgroup analyses by HER2 status suggest that the benefit of eribulin therapy was preserved in this population (HR = 0.76; 95% CI = 0.47 to 1.26). In addition, patients in the eribulin arm whose tumors tested negative for HER2, estrogen receptor, and progesterone receptor over-expression displayed a trend toward improved overall survival (HR = 0.81; 95% CI: 0.46 to 1.10). Similarly, trends toward an improvement in OS were seen in patients randomized to the eribulin arm who had been previously treated with more than three prior

chemotherapy regimens in any setting and in patients with metastatic disease involving more than two organs.

Table 27: Subgroup Analyses of Overall Survival for Study 305 (adapted from FDA statistical review)

Subgroups	N		Median (95% CI)		HR (95% CI)
	Eribulin	TPC	Eribulin	TPC	
N. America / W. Europe / Australia	325	163	13.1 (11.8,14.7)	10.1 (8.4,10.9)	0.73 (0.57, 0.92)
USA	100	46	13.1 (10.7,15.3)	10.7 (7.0,18.0)	0.93 (0.59, 1.46)
w/ Prior Capecitabine Treatment	370	189	12.9 (11.7,14.3)	10.1 (7.7,11.4)	0.77 (0.61, 0.97)
w/o Prior Capecitabine Treatment	138	65	13.4 (11.1,18.4)	12.0 (10.0, NE)	0.94 (0.62, 1.44)
HER2/neu Positive	83	40	11.3 (9.4,12.3)	9.1 (7.3, 13.0)	0.76 (0.47, 1.26)
HER2 + & >3 Chemos	49	23	11.5 (9.3,12.3)	9.1 (7.2,13.1)	0.77 (0.41, 1.43)
HER2/neu Negative	373	192	13.2 (12.1, 14.7)	10.5 (8.4,14.2)	0.81 (0.64, 1.02)
Triple Negative	93	51	9.5 (7.1,13.8)	7.0 (4.7,8.9)	0.71 (0.46, 1.10)
w/ Prior >3 Chemos	264	139	12.5 (10.7,13.8)	10.2 (8.2,13.0)	0.84 (0.64, 1.10)
w/ >3 Chemos in Metastatic setting	117	73	11.7 (9.2,13.8)	10.0 (6.0,14.6)	0.90 (0.60, 1.35)
w/ >2 Organs Involved	133	84	9.2 (7.6,11.1)	6.8 (5.7,10.3)	0.81 (0.57, 1.17)

Table 28 shows the post-hoc subgroup analyses using updated survival data submitted by the applicant on July 28, 2010. Overall, the results of these analyses were similar to the original subgroup analyses based upon the pre-specified data cut-off point (refer to Section 6.1.3 for details regarding the updated OS analysis). Of note, the subgroup analysis of the HER2⁺ population based upon the updated survival data showed a large trend in the point estimate toward improved survival in the eribulin arm (p = 0.015; HR = 0.594, 95% CI: 0.389 to 0.907).

Table 28: Summary of Overall Survival by Subgroup Using Updated Overall Survival Data (copied from applicant submission)

Overall Survival		Eribulin N=508	TPC N=254
North America/Western Europe/Australia			
	Number of patients events	325/252	163/132
	Median	402 days	308 days
	(95% CI)	(359 - 451)	(255 - 332)
	Hazard Ratio ^a (95% CI)	0.791 (0.639 - 0.980)	
	<i>P</i> value ^b (Log rank)	0.031	
Eastern Europe			
	Number of patients events	129/90	64/50
	Median	409 days	383 days
	(95% CI)	(365 - 495)	(308 - 533)
	Hazard Ratio ^a (95% CI)	0.882 (0.620 - 1.255)	
	<i>P</i> value ^b (Log rank)	0.485	
Latin America/South Africa			
	Number of patients events	54/44	27/21
	Median	282 days	340 days
	(95% CI)	(268 - 489)	(210 - 393)
	Hazard Ratio ^a (95% CI)	0.719 (0.410 - 1.260)	
	<i>P</i> value ^b (Log rank)	0.248	
Her2 Positive			
	Number of patients events	83/66	40/37
	Median	359 days	272 days
	(95% CI)	(311, 446)	(240, 326)
	Hazard Ratio ^a (95% CI)	0.594 (0.389, 0.907)	
	<i>P</i> value ^b (Log rank)	0.015	
Her2 Negative			
	Number of events	373/285	192/151
	Median	409 days	319 days
	(95% CI)	(367, 448)	(256, 380)
	Hazard Ratio ^a (95% CI)	0.849 (0.695, 1.036)	
	<i>P</i> value ^b (Log rank)	0.106	
Her2 Unknown			
	Number of patients events	52/35	22/15
	Median	458 days	423 days
	(95% CI)	(320, 573)	(308, 742)
	Hazard Ratio ^a (95% CI)	0.917 (0.481, 1.745)	
	<i>P</i> value ^b (Log rank)	0.791	
Previous Capecitabine – Yes			
	Number of patients events	370/291	189/154
	Median	395 days	308 days
	(95% CI)	(355, 421)	(235, 356)
	Hazard Ratio ^a (95% CI)	0.787 (0.645, 0.961)	
	<i>P</i> value ^b (Log rank)	0.018	
Previous Capecitabine – No			
	Number of patients events	138/95	65/49
	Median	454 days	346 days
	(95% CI)	(346, 556)	(304, 535)
	Hazard Ratio ^a (95% CI)	0.865 (0.606, 1.233)	
	<i>P</i> value ^b (Log rank)	0.421	

In Study 305, some patients on the TPC arm received study therapy to which they had already been exposed. Twenty-nine percent of TPC patients received a drug in the same class as a prior therapy, 14% received the same drug that they had already received, and 1% of TPC patients received a therapy that they had progressed on. Therefore, an exploratory analysis was conducted to explore whether the OS results were potentially confounded by the retreatment of some TPC patients with chemotherapy to which they had already been exposed. In this analysis, patients in both the TPC and eribulin arms who were assigned to receive a chemotherapy regimen of the same class that they had previously received prior to randomization were subtracted from the ITT population. In the subgroup of patients who either received or were assigned to receive a new class of anti-cancer therapy, the OS benefit was similar in patients who were treated with eribulin (HR =0.70, with 95% confidence intervals with an upper bound below 1 for both subgroups). *Comment: The results of this exploratory analysis are supportive of the primary analysis in that the HR was not affected by whether or not subjects were included who had received the same therapy previously to the therapy assigned in Study 305.*

Table 29: Subgroup Analyses Based Upon Repetition of Therapy in Study 305
(adapted from FDA statistical review)

Subgroups	N		Median (95% CI)		HR (95% CI)
	Eribulin	TPC	Eribulin	TPC	
Assigned Study 305 Therapy Not Previously Received in Any Setting	362	180	13.6 (12.0,14.9)	10.2 (8.4,12.0)	0.70 (0.55, 0.89)
Assigned Study 305 Therapy Not Previously Received in the Metastatic Setting	419	204	13.2 (12.0,14.7)	10.2 (8.4,11.4)	0.70 (0.56, 0.87)

Comment: Study 305 was not designed to detect differences between the treatment groups within subgroups. In general, the results of these subgroup analyses should be interpreted with caution, given the relatively small sample size of most of the subgroups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Refer to the discussion of efficacy for Study 201 in Section 6.1.10 for a review of clinical information relevant to dosing recommendations.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to the analyses of OS, PFS, and duration of response in Sections and 6.1.4 and 6.1.5 for a review of the persistency of efficacy effects.

6.1.10 Additional Efficacy Issues/Analyses

Supportive efficacy results from two single arm studies of eribulin in patients with advanced breast cancer, Studies 201 and 21, are described in this section of the review. Please refer to Section 5.3.2 for details regarding the design of these studies.

Study 201

Study 201 was a single arm, open-label study of eribulin in 104 U.S. patients with advanced metastatic breast cancer who had previously been treated with an anthracycline and a taxane. Enrolled patients were required to have measurable disease by RECIST and have developed progressive disease within six months of their last cytotoxic chemotherapy regimen. Two cohorts of patients were enrolled. Seventy-one patients were enrolled in the first cohort to receive eribulin at a dose of 1.4 mg/m² on Days 1, 8 and 15 of a 28-day cycle. A second cohort of patients was added due to the high incidence of neutropenia requiring dose adjustments and delays in the 28-day cohort; this second cohort enrolled 33 patients to receive the same eribulin dose on Days 1 and 8 of a 21-day cycle.

The baseline demographic information and disease characteristics for patients enrolled in Study 201 are summarized in Table 30.

Table 30: Baseline Demographic and Disease Characteristics of Patients Enrolled in Study 201 (adapted from clinical study report)

Patient Characteristics	28-Day Schedule N = 70	21-Day Schedule N = 33	Total (N=762)
Age (years)			
Mean (sd)	56 (11)	55 (11)	55 (11)
Median (range)	55 (34 – 84)	52 (32 – 81)	55 (32 – 84)
<65 (%)	53 (76)	27 (82)	80 (78)
>= 65 (%)	17 (24)	6 (18)	23 (22)
Race (n, %)			
White	51 (73)	21 (64)	72 (70)
Hispanic	9 (13)	3 (9)	12 (12)
Black	5 (7)	6 (18)	11 (11)
Asian/Pacific Islander	3 (4)	2 (6)	5 (5)
Other	2 (3)	1 (3)	3 (3)

Patient Characteristics	28-Day Schedule N = 70	21-Day Schedule N = 33	Total (N=762)
ECOG Performance status, n (%)			
0	29 (41)	18 (55)	47 (46)
1	41 (59)	15 (46)	56 (54)
Estrogen receptor status, n (%)			
Positive	46 (66)	17 (52)	63 (61)
Negative	22 (31)	16 (49)	38 (37)
Unknown/not done	2 (3)	0 (0)	2 (2)
Progesterone receptor status, n (%)			
Positive	37 (53)	11 (33)	48 (47)
Negative	31 (44)	22 (67)	53 (52)
Unknown/not done	2 (3)	0 (0)	2 (2)
HER2 receptor status, n (%)			
Positive	9 (13)	5 (15)	14 (14)
Negative	55 (79)	27 (82)	82 (80)
Unknown	6 (9)	1 (3)	7 (7)
ER⁺, PR⁺, HER2⁻, n (%)	19 (27)	11 (33)	30 (29)

Patients enrolled in Study 201 received a median of 4 prior treatment regimens. All patients had previously received an anthracycline and a taxane, and 68% had prior capecitabine exposure. Eighty-six percent of patients had received prior radiotherapy.

Comment: Baseline demographic and disease characteristics of patients enrolled in Study 201 were similar to those of patients enrolled in Study 305 with respect to age, ECOG status, and HER2 status. However, a smaller percentage of patients enrolled in Study 201 were White (92% of patients in Study 305 compared to 70% of patients in Study 201). In addition, a lower proportion of patients had estrogen or progesterone positive tumors (ER⁺: 70% in Study 305 compared to 61% in Study 201; PR⁺: 56% in Study 305 compared to 47% in Study 201). A higher percentage of patients enrolled in Study 201 had tumors that were triple negative (20% in Study 305 compared to 29% in Study 201). Finally, Study 201 was conducted solely in the United States, whereas 19% of enrolled patients in Study 305 were from the United States.

The primary efficacy endpoint of Study 201 was objective response rate in the per protocol population according to an independent review. The per protocol population included patients who met the key enrollment criteria of measurable disease that had progressed within 6 months of prior chemotherapy treatment. Table 31 summarizes the best objective response to eribulin by independent review for the per protocol population. All objective responses were partial responses. Patients enrolled in the cohort that received a 21-day schedule of eribulin achieved a higher rate of objective response.

Table 31: Objective Response by Independent Review: Study 201 (Per Protocol Population) (adapted from FDA statistical analysis)

	28-Day Schedule N=59 (%)	21-Day Schedule N=28 (%)
Objective Response Rate (CR+PR)	6 (10)	4 (14)
Complete Response (CR)	0	0
Partial Response (PR)	6 (10)	4 (14)
Stable Disease (SD)	21 (36)	16 (57)
Progressive Disease (PD)	29 (37)	7 (25)
Unknown (UN)	3 (5)	1 (4)

The median duration of response based upon independent review for those patients with partial responses was 153 days (range: 114 to 363 days) for the 28-day cohort and was not evaluable in the 21-day cohort.

In summary, the ORR observed in Study 201 was supportive of the effect observed in Study 305.

Study 211

Study 211 was an open-label, single-arm study of eribulin in 299 patients with locally advanced or metastatic breast cancer who were previously treated with chemotherapy including an anthracycline, a taxane, and capecitabine therapy. Enrolled patients were also required to have measurable disease that proved refractory to the most recently administered chemotherapy. The study was conducted in the United States and the European Union. The primary efficacy endpoint of this trial was objective response rate of the eligible population by independent review. The eligible population consisted of patients who received at least one dose of eribulin and met major eligibility criteria. To be considered part of the eligible population, HER2+ patients must have been treated previously with trastuzumab.

Table 32 summarizes the baseline demographic information and disease characteristics of patients included in the eligible population for Study 211. Patients received a median of four prior chemotherapy regimens, and 100% of patients had received prior taxane, anthracycline, and capecitabine therapy.

Table 32: Baseline Demographic and Disease Characteristics of Eligible Patients Enrolled in Study 211 (adapted from clinical study report)

Patient Characteristics	Eligible Population (N=269)
Age (years)	
Mean (sd)	55 (11)
Median (range)	56 (26 – 80)
<65 (%)	217 (81)
>= 65 (%)	52 (19)
Race (n, %)	
White	187 (70)
Black	12 (5)
Asian/Pacific Islander	6 (2)
Other	7 (3)
Missing ^a	57 (21)
ECOG Performance status, n (%)	
0	100 (37)
1	152 (57)
2	16 (6)
Estrogen receptor status, n (%)	
Positive	183 (68)
Negative	83 (31)
Unknown/not done	3 (1)
Progesterone receptor status, n (%)	
Positive	129 (48)
Negative	119 (44)
Unknown/not done	21 (8)
HER2 receptor status, n (%)	
Positive	29 (11)
Negative	224 (83)
Unknown	16 (6)
ER⁺, PR⁺, HER2⁺, n (%)	54 (20)

^a Information regarding race was not collected in France due to regulatory constraints

Baseline demographic and disease characteristics of patients enrolled in Study 201 were generally similar to those of patients enrolled in Study 305. Unlike Study 305, in which 73% of enrolled patients had been previously exposed to capecitabine, 100% of eligible patients in Study 211 had received prior capecitabine therapy.

Table 33 summarizes the best objective response to eribulin by independent review for the Per Protocol Population of Study 211. The objective response rate (ORR) was 9% for the eligible population and all objective responses were partial responses. The ORR by independent review for the ITT population was also 9%.

Table 33: Objective Response Rate by Independent Review: Study 211 (adapted from FDA statistical analysis)

	Eligible Population N=269 n (%)
Objective Response Rate (CR+PR)	25 (9)
Complete Response (CR)	0 (0)
Partial Response (PR)	25 (9)
Stable Disease (SD)	125 (47)
Progressive Disease (PD)	116 (43)
Not Evaluable (NE)	3 (1)

The median duration of response based upon independent review for those patients with partial responses was 126 days (range: 86 to 177 days).

The ORR (9%) observed in Study 211 was slightly less than the ORR observed in Study 305 (11%). The duration of response was similar in the two studies.

In summary, the ORR and duration of response observed in Study 211 provide supportive evidence of the efficacy of eribulin in heavily-pretreated patients with advanced breast cancer.

Pooled Analyses Conducted by Applicant

The integrated summary of efficacy submitted by the applicant presented analyses of pooled efficacy data for Studies 201, 211, and 305. In these analyses, patients who received at least one dose of eribulin, excluding Study 201 patients who were enrolled in the first cohort to receive the 28-day cycle of eribulin, were pooled. Table 34 shows that the ORR in the pooled analysis (10.8%) was similar to the ORR in the eribulin-treated population in study 305 (11.3%).

Table 34: Applicant’s Analysis of Best Overall Response and Objective Response Rate by Independent Review (Eribulin Treated Population) (copied from ISE submission)

	Studies ^a 201 ^b , 211 ^b and Study 305 Eribulin Treated ^c N = 827	Study 305 Eribulin Treated ^c N = 503
CR, n (%)	3 (0.4)	3 (0.6)
PR, n (%)	86 (10.4)	54 (10.7)
SD, n (%)	360 (43.5)	209 (41.6)
PD, n (%)	322 (38.9)	190 (37.8)
NE/unknown, n (%)	56 (6.8)	47 (9.3)
ORR (CR + PR), n (%)	89 (10.8)	57 (11.3)
95% CI ^d	8.7, 13.1	8.7, 14.4

Abbreviations: CI = confidence interval; CR = complete response; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

^a Pooled results from Studies 305 (eribulin treated), 211 and 201 (21-day cycle treatment group only).

^b If a patient was not independently reviewed then the Investigators’ assessment was used for Study 201 and 211 in cases where patients progressed on or before their Cycle 2 assessments

^c For Study 305, data for the eribulin-treated arm only are included.

^d Exact 2-sided 95% CI.

Similarly, Table 35 shows that the pooled analysis of duration of response conducted by the applicant was similar to the duration of response observed in eribulin-treated patients in Study 305.

Table 35: Applicant’s Analysis of Duration of Response by Independent Review (Eribulin Treated Population) (copied from ISE submission)

Duration of Response (days)	Studies ^a 201, 211 and Study 305 Eribulin Treated ^b	Study 305 Eribulin Treated ^b
Number of responders	89	57
Number of patients who progressed or died (%)	49 (55.1)	31 (54.4)
Number of patients censored (%)	40 (44.9)	26 (45.6)
Min, max ^c	0+, 480+	0+, 305+
Median	142	145
95% CI	126, 168	125, 176

Abbreviations: CI = confidence interval; max = maximum; min = minimum.

^a Pooled results from Studies 305, 211 and 201 (21-day cycle treatment group only).

^b For Study 305, data for the eribulin-treated arm only are included.

^c “+” indicates patient observation was censored.

Other Exploratory Analyses

An additional exploratory analysis was conducted to assess whether the improvement in OS observed in the eribulin arm could be partially explained by investigator bias to treat patients more aggressively with chemotherapy after discontinuation from Study 305. Of the patients who discontinued study therapy for reasons other than death, 68% of patients in the eribulin arm and 62% of patients in the TPC arm received chemotherapy after discontinuation from Study 305. In addition, 13% of patients in the eribulin arm and 18% of patients in the TPC arm received hormonal therapy after discontinuing study therapy.

Comment: although there are slight differences in the percentages of patients who received chemotherapy and hormonal therapy after discontinuation from Study 305, these differences were not of sufficient magnitude to raise concerns that there was an investigator bias to treat TPC patients less aggressively than eribulin patients.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The database used to evaluate safety reflected adverse events collected from 1,222 eribulin-treated patients in 11 completed studies. In addition, summary data from five additional ongoing studies conducted by the applicant and interim data from eight ongoing NCI studies were reviewed. This safety review focused primarily on results from Study 305, the only completed randomized study submitted with this NDA. Review of safety data from the additional 719 subjects focused on for the exploration of additional safety signals that were not evident in Study 305.

7.1.2 Categorization of Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) version 10.0 was used to code all adverse events in Study 305.

The Study 305 adverse event dataset contained 10,616 individual adverse event listings. A total of 693 verbatim terms described all 10,616 adverse events. 10,384 adverse events described by 676 verbatim terms were considered by the applicant to be treatment-emergent.

Review of verbatim terms in the adverse event dataset to determine whether MedDRA preferred terms were appropriately coded revealed no instances of inaccurate coding. In addition, Case Report Forms (CRFs) for 62 patients enrolled in Study 305 were reviewed

(25% of the patients for which CRFs were submitted) to determine if verbatim terms, toxicity grading, intervention, and characterization of seriousness of adverse events were characterized appropriately in the CRFs and accurately entered into the database. In general, any discrepancies between the CRFs and database entries or inaccuracies noted in the characterization of adverse events in the CRFs were resolved upon detailed review of the numerous data clarification forms submitted by the applicant with the case report forms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The primary analysis of safety was performed using the adverse event data set from Study 305, in which 503 patients were treated with eribulin. In addition, pooled safety data from the 827 breast cancer patients treated in Studies 305, 201, and 211 who received the targeted eribulin dose, and pooled data from all eribulin-treated patients (1,222) were analyzed and compared with the safety data from study 305 to explore additional safety signals.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Clinical studies of eribulin generally limited enrollment to patients with ECOG performance status of 2 or better who had adequate bone marrow, renal, and hepatic function. Additionally, study 305 excluded patients with significant cardiovascular impairment, HIV positive status, and Grade 3 and above pre-existing neuropathies. There is inadequate data to assess the safety of eribulin therapy for patients who do not meet these criteria. However, the baseline characteristics required of patients enrolled in studies of eribulin are typical of those required in studies of other cytotoxic agents. In addition, the number of eribulin-treated patients in study 305 is comparable to the safety database submitted for other approved chemotherapeutic agents. For example, the safety database included in the original approval for ixabepilone reflected its use in 495 breast cancer patients (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022065s002lbl.pdf, accessed on 7/27/2010).

Comment: Based upon FDA precedent, the safety database submitted with this NDA contained an adequate number of patients for consideration of approval for treatment of patients with refractory metastatic breast cancer, a life-threatening malignancy.

7.2.2 Explorations for Dose Response

Study 503

In study 503, patients could continue eribulin therapy until disease progression, patient death, or discontinuation from the study for other reasons including unacceptable toxicity. Table 36 outlines the number of cycles of therapy completed by patients in the eribulin and TPC groups, and Table 37 compares the duration of therapy in the two groups. In general, patients in the eribulin group completed more cycles of therapy and remained on treatment longer than patients in the TPC group. Fifty-eight percent of eribulin treated patients received 5 or more cycles of therapy and the median duration of therapy was 118 days.

Table 36: Number of Cycles of Therapy Received by Patients in Study 305

Number of Cycles	Eribulin N=503		TPC N=247	
	n	%	n	%
1	21	4	33	13
2	60	12	60	24
3	96	19	45	18
4	31	6	20	8
5	51	10	14	6
6	59	12	32	13
7	26	5	7	3
8	30	6	7	3
9	34	7	4	2
10	22	4	8	3
11	18	4	3	1
12	9	2	3	1
13	11	2	1	0
14	8	2	1	0
15	6	1	1	0
16	10	2	2	1
17	2	0	1	0
18	1	0	0	0
19	0	0	1	0
20	4	1	1	0
21	2	0	1	0
22	0	0	1	0
23	2	0	0	0
31	0	0	1	0

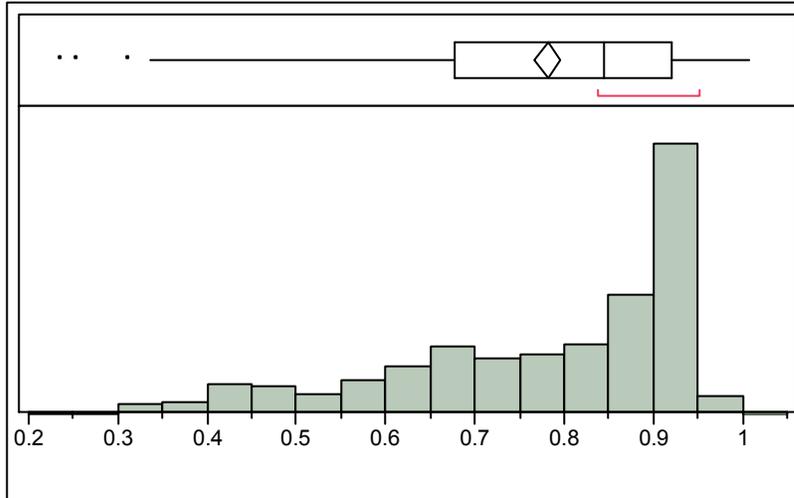
Table 37: Duration of Therapy in Study 305

Exposure	Eribulin N=503 n (%)	TPC N=247 n (%)
Number of cycles completed n(%)		
1-2	81 (16)	93 (38)
3-4	127 (25)	65 (26)
5-6	110 (22)	46(19)
>6	185 (37)	43 (17)
Median number of cycles completed (range)	5 (1-23)	3 (1-31)
Mean number of cycles completed (std dev)	6 (4)	4 (4)
Duration (days)		
Mean (std dev)	137 (92.6)	98 (94.3)
Median (min,max)	118 (21,497)	63 (1,644)

The Study 305 protocol contained dose adjustment guidelines for patients who incurred specific toxicities. In the eribulin group, 249 of 503 (50%) patients required dose delay at some point during therapy, compared to 98 (40%) patients in the control group. One hundred forty-five (29%) and 63 (26%) patients required dose reduction in the eribulin and control groups, respectively. Finally, 28 (6%) patients receiving eribulin required dose interruption, compared to 23 (9%) patients in the TPC group.

Figure 8 and Figure 9 depict the dose-intensity (mg/m²/week) and the relative dose-intensity for eribulin-treated patients in study 305. The median dose intensity was 0.85 mg/m²/week (compared to an expected dose intensity of 0.93 mg/m² if patients received 1.4 mg/m² twice during each 21 day cycle), and the relative dose-intensity was 0.91.

Figure 8: Eribulin Dose Intensity (mg/m²/week)



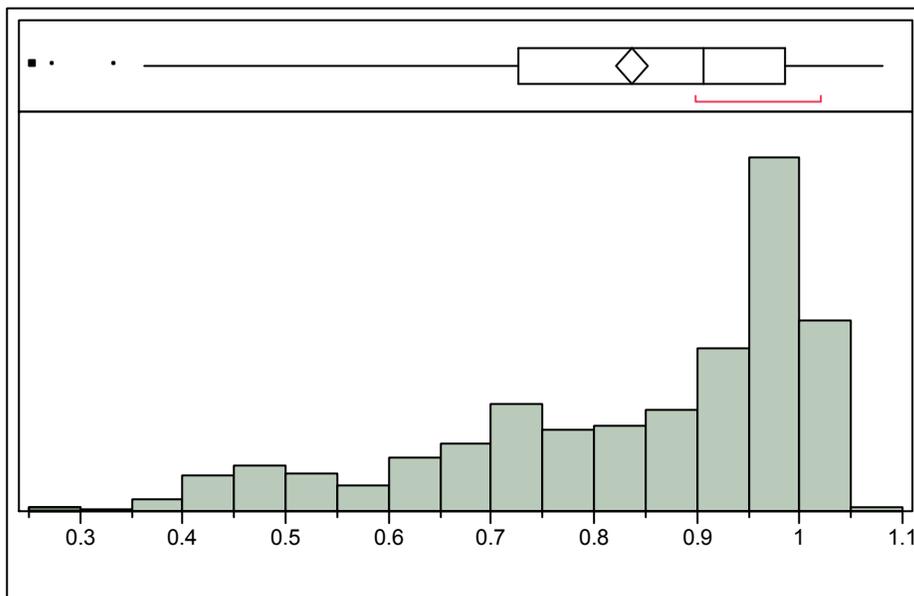
Quantiles

100.0%	maximum	1.0077
99.5%		0.9721
97.5%		0.9495
90.0%		0.9370
75.0%	quartile	0.9198
50.0%	median	0.8458
25.0%	quartile	0.6781
10.0%		0.5075
2.5%		0.3919
0.5%		0.2836
0.0%	minimum	0.2366

Moments

Mean	0.781281
Std Dev	0.1662851
Std Err Mean	0.0074217
upper 95% Mean	0.7958624
lower 95% Mean	0.7666996
N	502

Figure 9: Eribulin Relative Dose Intensity



Quantiles

100.0%	maximum	1.0801
99.5%		1.0419
97.5%		1.0177
90.0%		1.0043
75.0%	quartile	0.9859
50.0%	median	0.9065
25.0%	quartile	0.7268
10.0%		0.5440
2.5%		0.4201
0.5%		0.3040
0.0%	minimum	0.2536

Moments

Mean	0.8373859
Std Dev	0.1782262
Std Err Mean	0.0079546
upper 95% Mean	0.8530144
lower 95% Mean	0.8217573
N	502

The median duration of therapy for patients in the eribulin arm (118 days) was longer than that of patients who received vinorelbine (50 days), gemcitabine (71 days), taxanes (88 days) and anthracyclines (57 days). The median duration of therapy for patients receiving capecitabine (119 days) was comparable to the median duration of therapy for eribulin-treated patients.

Comment: The relative eribulin dose intensity achieved by patients in Study 305 appears reasonable. Furthermore, although eribulin-treated patients required more dose delays

than patients in the control group, they received more cycles of chemotherapy and remained on therapy longer than patients in the control group

7.2.3 Special Animal and/or In Vitro Testing

Carcinogenicity studies have not been conducted with eribulin. Eribulin was not mutagenic in an *in vitro* bacterial reverse mutation assay (Ames test). Eribulin was positive in mouse lymphoma mutagenesis assays, and was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

Nonclinical findings in repeated-dose dog and rat toxicology studies suggest that male fertility may be compromised by treatment with eribulin. Rats exhibited testicular toxicity (hypocellularity of seminiferous epithelium with hypospermia/aspermia) following dosing with eribulin at or above 0.42 times the recommended human dose (mg/m^2) administered once weekly for 3 weeks, or at or above 0.21 times the recommended human dose (mg/m^2) administered once weekly for 3 out of 5 weeks, repeated for 6 cycles. Testicular toxicity was also observed in dogs administered 0.64 times the recommended human dose (mg/m^2) weekly for 3 out of 5 weeks, repeated for 6 cycles.

A developmental toxicity study was performed in pregnant rats, who received intravenous infusions of eribulin at doses approximately 0.04, 0.12, 0.42 and 0.64 times the recommended human dose, based on body surface area (mg/m^2) on gestation days 8, 10, and 12 (which corresponds to the period of fetal organogenesis). Increased abortion and severe external or soft tissue malformations were observed in offspring at doses 0.64 times the recommended human dose based on body surface area (mg/m^2), including the absence of a lower jaw, absence of a tongue, absence of stomach, and absence of spleen. Increased embryo fetal death/resorption, reduced fetal weights, and minor skeletal anomalies consistent with developmental delay were also reported at or above doses of 0.42 times the recommended human dose. In addition, maternal toxicity was reported in rats at or above doses of 0.42 times the recommended human dose (mg/m^2); toxicities noted in maternal rats included enlarged spleen, reduced weight gain, and decreased food consumption.

7.2.4 Routine Clinical Testing

Refer to sections 7.4.2 (laboratory monitoring) and 7.4.4 (ECG) for discussion on the adequacy of hematology monitoring, chemistry monitoring, and ECG monitoring during study 503.

7.2.5 Metabolic, Clearance, and Interaction Workup

In Study 103, a Phase 1 radiotracer mass-balance and treatment study, six subjects with advanced solid tumors received 2 mg ^{14}C -eribulin on Day 1 of the first cycle. Unchanged

eribulin was the major circulating species in plasma following administration of ¹⁴C-eribulin to patients, with metabolite concentrations represented <0.6% of parent compound. After administration of ¹⁴C-eribulin to patients, approximately 82% of the dose was eliminated in feces and 9% in urine, indicating that renal clearance is not a major route of eribulin elimination. Eribulin accounted for approximately 88% of the dose eliminated in feces and approximately 91% of the dose eliminated in urine.

In vitro studies indicate that cytochrome P450 3A4 (CYP3A4) has only a negligible role in the metabolism of eribulin. Eribulin inhibited CYP3A4 activity in human liver microsomes, but did not significantly inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 at concentrations up to 5 μM in pooled human liver microsomes. In addition, eribulin did not demonstrate a potential to induce CYP1A, CYP2C9, CYP2C19, and CYP3A in studies in primary human hepatocytes. *In vitro* drug interaction studies indicated that eribulin did not inhibit drugs that were substrates of these enzymes. *In vitro* studies demonstrated that eribulin is a substrate and a weak inhibitor for the drug efflux transporter P-gp.

The effect of ketoconazole, a strong inhibitor of cytochrome P450 3A4 (CYP3A4), on the pharmacokinetics (PK) of eribulin was studied in an open-label crossover trial in 12 patients with advanced solid tumors. The mean dose-normalized AUC was similar when eribulin was administered in combination with ketoconazole compared to when eribulin was administered alone (ratio of the mean AUC: 0.97; 90% CI: 0.83, 1.12).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Analyses of the following important adverse reactions that are associated with other drugs that disturb microtubule function are included in other sections of this review: cytopenias, hypersensitivity reactions, gastrointestinal disturbances, peripheral neuropathy, cardiac dysfunction, and hepatic dysfunction.

Tissue extravasation injury, which can occur with vinca alkaloids, was reported in one eribulin patient enrolled in Study 202. This patient developed Grade 3 extravasation injury during eribulin administration in Cycle 6. The event resolved with sequelae, was not considered serious, and did not lead to discontinuation of eribulin therapy.

7.3 Major Safety Results

7.3.1 Deaths

Overview of the applicant's methods

Eisai analyzed deaths separately by study and then performed a pooled analysis for patients in studies 503, 201, and 211 who received the 1.4 mg/m² eribulin dose at the same dosing schedule (Days 1, 8 of in 21 day cycle). For studies 211 and 201, survival was a secondary endpoint. The applicant provided analyses of deaths that occurred within 30 days of the last eribulin dose or within 30 days of the study termination visit, whichever was longer.

Because overall survival was the primary endpoint of study 305, all patients were followed for survival every 3 months after discontinuation from study therapy to obtain data on survival. For studies 201 and 211, patients were followed for 30 days after the last eribulin dose for toxicities, and investigators were instructed to follow patients for survival every 3 months thereafter.

Comment: The applicant's approach to follow up and evaluate deaths appears reasonable; however, this reviewer elected to analyze deaths occurring within 60 days of termination of study therapy in Study 305 to provide a more comprehensive analysis.

For Study 305, an analysis of death causality occurred for all patients who had died as of the data cut-off (May 12, 2009), with an emphasis on patients who died within 30 days of the last eribulin dose or whose death was associated with an adverse event. Detailed narratives of all patient deaths occurring within 30 days were provided for both treatment arms, irrespective of whether the deaths were associated with SAEs. Eight patients enrolled in the study were excluded from the analysis because they died before receiving treatment (4 in the eribulin arm and 4 in the TPC arm).

Table 38: Patient Deaths Occurring Prior to Initiation of Study Therapy

Arm	Site	Patient ID	Age	Randomization Date	Date of Death	Cause of Death
eribulin	1103	1005	54	11/09/2007	(b) (6)	Progressive Disease
TPC	1104	1006	48	02/11/2008		Progressive Disease
TPC	1401	1014	43	07/11/2007		Progressive Disease
TPC	1703	1004	61	07/17/2007		Progressive Disease
TPC	2003	1002	44	10/27/2008		Progressive Disease
eribulin	2008	1017	56	03/05/2008		Progressive Disease

Arm	Site	Patient ID	Age	Randomization Date	Date of Death	Cause of Death
eribulin	2502	1004	46	08/15/2007	(b) (6)	Progressive Disease
eribulin	3011	1002	57	07/08/2008		Progressive Disease

FDA review of deaths

Summary of Deaths - Study 305 (as of May 12, 2009)

In study 305, 271 (53.9%) eribulin-treated patients and 143 (57.9%) patients in the TPC group had died as of the data cutoff. In both arms, the primary cause of death for the majority of patients was progressive disease (254 [50.5%] and 135 [54.7%] of patients in the eribulin and TPC groups, respectively). In some cases, patients who died of progressive disease also experienced SAEs. Seventeen patients (3%) in the eribulin group and 8 patients (3%) in the TPC group died for reasons other than progressive disease according to the investigator's assessment. One patient's death (patient number 20081018) was recorded as related to toxicity on Day 287; however, death occurred 238 days after her last eribulin dose and no adverse events leading to death were recorded. *Comment: given the long time interval between the last dose of eribulin and the patient's death, it is unlikely that this patient's death was related to eribulin therapy.*

The proportion of deaths within the first 30 days of treatment and first 60 days of treatment were comparable between the two treatment arms. Of the 271 (53.9%) eribulin-treated patients and 143 (57.9%) patients in the TPC group who died as of the data cutoff, only a fraction of patients died within a 30 or 60 day period (4.0 and 10.4 percent for eribulin and 7.7 and 16.2 percent for TPC). Table 39 illustrates that a higher percentage of patients died within 30 and 60 days of study therapy in the TPC (control) group compared to the eribulin group.

Table 39: Deaths Occurring Within 60 days of Study Therapy –Study 305

Days Elapsed from Last Treatment	Eribulin N=503 n (%)	TPC N=247 n (%)
0-30	20 (4.0)	19 (7.7)
31-60	32 (6.4)	21(8.5)

To verify the cause of death described by the applicant, narrative summaries and serious adverse event listings were reviewed. Additionally the adverse event dataset was reviewed to evaluate adverse events that occurred within 60 days of the patients' deaths to determine whether adverse events may have contributed to the cause of death. Table 40 and Table 41 provide a tabular listing of deaths that occurred within 60 days of receipt of study treatment in descending order of days since the last dose (bold type indicates that the death was considered by the applicant to be possibly related to study treatment,

shaded entries indicate additional deaths that this reviewer considers are possibly related to study therapy).

Three patients in the eribulin group and 2 patients in the TPC group died within 30 days of stopping therapy without an associated adverse event (13011018, 20021002, 28241003, all attributed to progressive disease) (*note: pt 2001002 also had "life threatening confusional state" thought to be due to neurological progression but was also hyponatremic (NA 122) at the time*).

Five of the 20 patients who died within 30 days of receipt of eribulin therapy experienced serious adverse events that were considered by the investigator possibly related to eribulin:

- Patient 11011003: died of febrile neutropenia 7 days after eribulin treatment
- Patients 20081016 and 25021012: died of pulmonary infections 11 and 12 days after treatment
- Patients 28241001 and 30021004 experienced dyspnea 15 and 12 days after eribulin treatment.

In addition, this reviewer identified one additional death occurring within 30 days of treatment and 2 additional deaths occurring within 31-60 days of therapy that may have been related to eribulin.

In contrast, 2 of the 19 patients who died within 30 days of receipt of TPC therapy experienced a serious adverse event reported by the investigator as possibly or probably related:

- Patient 23021006: died of febrile neutropenia 13 days after receipt of chemotherapy
- Patient 14051020: died of invasive aspergillosis 11 days after the last taxane treatment

In addition, this reviewer identified one additional death occurring within 30 days of treatment and 1 additional deaths occurring within 31-60 days of therapy that may have been related to therapy in the control group.

Table 40: Tabular Listing of Deaths Occurring within 60 days of Eribulin Therapy – Study 305^{a,b}

Site	Patient ID	Age	Number of Cycles	Days since Last Dose	Brief Description of Probable Cause of Death
2008	1009	71	1	5	s/p 2 doses of eribulin, patient developed diabetic ketoacidosis; past medical history of Type 2 DM, diabetic retinopathy.
1101	1003	56	2	7	febrile neutropenia with shock; had previous dose reduction for neutropenia one month prior
2002	1002	60	1	7	Progressive disease; Death 7 days after first dose of eribulin. SAE confusional state with multiple metastatic cerebral lesions reported 2 days prior to death.
2905	1004	45	2	8	H/O Type II DM. Non-neutropenic sepsis, presenting with hyperglycemia, hypotension, abdominal pain. WBC: 33K Developed renal failure with Cr 5.2. Disease progression by physical exam. <i>Reported by investigator as unrelated to eribulin, but there is a reasonable possibility that sepsis was related to chemotherapy.</i>
2008	1016	52	3	11	Cause of death mucositis, causing pulmonary infection
1301	1018	66	1	11	Progressive disease
2008	1031	44	7	12	Pulmonary thromboembolism; patient had femur fracture 1 month prior to event.
2502	1012	55	2	12	Febrile neutropenia, bronchopneumonia, <i>B. fragilis</i> septicemia
3002	1004	53	1	12	SAE dyspnea 11 days after C1D8 dose; No details about etiology in CRFs. Gr 1 dyspnea, PMH of allergy-induced asthma noted at screening. Dyspnea worsened with study treatment and was ongoing at the time of death; event reported as possibly related to study treatment.
2205	1004	38	4	14	Respiratory failure due to progressive disease, tumor related deterioration
2824	1001	60	1	15	Dyspnea accompanied by mild dehydration and pronounced weakness, without X-ray changes; worsening hepatic metastases; investigator reported possibly related to study drug.
1509	1002	52	2	16	Progressive disease
2413	1004	50	5	16	Progressive disease

Site	Patient ID	Age	Number of Cycles	Days since Last Dose	Brief Description of Probable Cause of Death
1904	1005	35	6	17	Progressive disease
2302	1005	48	1	17	Progressive disease
1807	1001	59	3	21	Progressive disease
1911	1001	69	6	23	Cardiovascular insufficiency, progressive disease
1401	1007	67	3	24	General health deterioration, progressive disease
2303	1002	69	4	25	11 days after C4D1, patient developed dyspnea – not related per investigator; PMH COPD
2824	1003	61	6	30	Progressive disease
1704	1001	54	3	31	Developed respiratory failure 23 days after C3D8 dose; pleural effusion noted on CT; deemed not related to study drug by investigator
2403	1012	39	3	32	Progressive disease
1102	1006	68	8	34	11 days after C8, D1 general health deterioration reported, deemed unrelated to study treatment by investigator
1409	1003	51	2	34	Progressive disease; “general health deterioration” recorded as fatal event
2403	1016	68	6	34	Progressive disease
2409	1005	53	1	34	Progressive disease noted as cause of death, but also had ongoing pneumonia with pleural effusion that led to treatment discontinuation 13 days after C1 D8 eribulin dose; <i>deemed unrelated by investigator, but may have been caused by study drug</i>
2302	1001	63	5	35	Progressive disease associated with SAE of depressed level of consciousness
1401	1018	44	4	36	Progressive disease associated with SAE of paraplegia
1911	1012	45	1	36	Progressive disease
1302	1012	30	3	38	Progressive disease
2829	1001	53	2	38	Progressive disease
2908	1002	32	9	38	Progressive disease
1103	1004	72	2	39	Progressive disease associated with SAE of lymphangitis
1402	1022	47	5	42	Progressive disease
2602	1002	44	1	45	Progressive disease
1402	1010	67	4	47	Progressive disease
1706	1002	68	4	47	Progressive disease
1902	1002	48	3	47	Progressive disease

Site	Patient ID	Age	Number of Cycles	Days since Last Dose	Brief Description of Probable Cause of Death
1903	1011	49	9	47	Grade 2 sensory neuropathy developed after three months of therapy; Grade 3 paresthesia and lower extremity pain were reported after 6 months of therapy. One week later, 16 days after C9 D1 dose, paraparesis developed (not graded), leading to discontinuation of eribulin. Progressive disease was reported as the cause of the paraparesis, although radiological confirmation of causality was not provided. Paraparesis was ongoing at time of death one month later, and considered fatal (47 days after last eribulin dose). <i>Primary cause of death determined to be progressive disease, but there is a possibility that neurologic toxicity due to eribulin contributed to paraparesis.</i>
2804	1001	75	5	47	Progressive disease
1301	1020	66	3	48	Progressive disease
1302	1011	34	6	49	Progressive disease
1604	1007	34	6	49	Progressive disease
2413	1002	59	4	51	Progressive disease; Gr 4 peripheral neuropathy ongoing at time of death
2905	1002	37	2	51	Progressive disease
2836	1001	46	2	52	Progressive disease
3001	1006	57	4	53	Progressive disease
2831	1009	64	9	54	Progressive disease
2702	1033	55	3	56	Progressive disease
2501	1004	59	5	57	Progressive disease
3005	1020	47	5	57	Progressive disease
2815	1004	41	1	59	Progressive disease
2205	1001	69	3	60	Progressive disease

^a. Bold type delineates deaths that the applicant reports are possibly related to study therapy

^b. Shaded entries indicate additional deaths identified by the reviewer as possibly related to study therapy.

Table 41: Tabular Listing of Deaths that occurred Within 60 days of TPC Treatment – Study 305^{a,b}

Site	Patient ID	Age	TPC Treatment Administered	Number of Cycles	Days since Last Dose	Brief Description of Probable Cause of Death
1601	1002	69	Capecitabine	1	0	<i>Although considered by the investigator to be unrelated to study therapy, pneumonia was diagnosed and death occurred on the same day as the Cycle 1, Day 4 dose; there is a reasonable possibility that death was related to therapy.</i>
1806	1002	54	Capecitabine	2	0	Progressive disease
1301	1004	52	Hormonals	1	6	Progressive disease
2828	1001	64	Taxanes	2	6	Progressive disease with pleural effusion
2205	1002	66	Gemcitabine	1	7	Pulmonary embolism
1906	1016	56	Gemcitabine	15	7	Progressive disease
1202	1005	58	Hormonals	1	10	Progressive disease, hepatic failure
1405	1020	73	Taxanes	1	11	Invasive aspergillosis
1704	1002	60	Capecitabine	1	12	Progressive disease, general health deterioration. Pt developed asthenia and diarrhea 4 days after study treatment. Diarrhea resolved two days prior to death but asthenia and general health deterioration persisted.
1706	1003	68	Capecitabine	1	12	Asthenia due to clinical progression
2302	1006	43	Etoposide	2	13	Febrile neutropenia, presumed sepsis
1302	1004	65	Gemcitabine	4	15	Pulmonary Embolism
2413	1005	52	Vinorelbine	10	18	Progressive disease
2008	1032	68	Vinorelbine	3	20	Progressive disease
2801	1001	45	Other	1	21	Dyspnea, progressive disease
3005	1018	42	Vinorelbine	3	23	Progressive disease associated with decreased performance status
1703	1003	35	Taxanes	1	27	Respiratory insufficiency

Site	Patient ID	Age	TPC Treatment Administered	Number of Cycles	Days since Last Dose	Brief Description of Probable Cause of Death
2402	1001	55	Gemcitabine	4	27	Dyspnea, clinically diagnosed progressive disease
1706	1010	52	Other	2	29	Progressive disease
2902	1001	66	Capecitabine	1	31	Progressive disease, abdominal pain due to liver nodule
2205	1003	68	Vinorelbine	2	35	Progressive disease
1408	1007	48	Vinorelbine	3	35	Progressive disease
2401	1002	46	Capecitabine	5	36	Progressive disease
1906	1023	60	Gemcitabine	3	37	Progressive disease
1706	1004	76	Gemcitabine	1	38	Progressive disease
2405	1010	59	Capecitabine	3	40	Progressive disease
1805	1005	36	Other	1	41	Progressive disease
2505	1003	60	Anthracyclines	6	43	Progressive disease
2409	1004	72	Taxanes	5	44	Progressive disease
2702	1030	48	Capecitabine	1	45	Progressive disease
2002	1005	51	Gemcitabine	1	49	Progressive disease
2812	1021	56	Gemcitabine	2	49	Progressive disease
1706	1008	60	Hormonals	3	50	Progressive disease
2808	1001	62	Capecitabine	2	51	Progressive disease
1102	1004	58	Capecitabine	3	52	Hemodynamic failure, associated with renal failure occurring 14 days after the cycle 3, day 14 dose; <i>reported by investigator as not related to capecitabine, but there is a reasonable possibility that hemodynamic instability and renal failure and were related to capecitabine therapy</i>
1704	1003	62	Capecitabine	5	53	Progressive disease
2505	1009	62	Vinorelbine	3	54	Progressive disease
1708	1001	61	Other	2	55	Progressive disease
2505	1011	62	Anthracyclines	2	57	Progressive disease
1301	1003	32	Vinorelbine	4	57	Progressive disease

^a. Bold type delineates deaths that the applicant reports are possibly related to study therapy

^b. Shaded entries indicate additional deaths identified by the reviewer as possibly related to study therapy.

Table 42 presents a summary of patient deaths within 60 days of therapy that were associated with adverse events by System Organ Class (SOC). With the exception of the

Nervous System Disorders SOC, the proportion of patients who experienced a death associated with an AE was equal to or less than that of the TPC arm.

Table 42: Patient Deaths Associated with Adverse Events by System Organ Class— Study 305

SOC	Eribulin N=503 n (%)			TPC N=247 n (%)		
	≤30 days	≥ 30 days	Total	≤30 days	≥ 30 days	Total
Blood and lymphatic system disorders ^a	1 (0.2)	0 (0)	1 (0.2)	1 (0.4)	0 (0)	1 (0.4)
General disorders and administration site conditions ^b	1 (0.2)	3 (0.6)	4 (0.8)	3 (1.2)	0 (0)	3 (1.2)
Hepatobiliary disorders ^c	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.4)
Infections and infestations ^d	3 (0.6)	1 (0.2)	4 (0.8)	2 (0.8)	0 (0)	2 (0.8)
Metabolism and nutrition disorders ^e	1 (0.2)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified ^f	4(0.8)	1 (0.2)	5 (1.0)	2 (0.8)	1 (0.4)	3 (1.2)
Nervous system disorders ^g	1 (0.2)	3 (.6)	4 (0.8)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders ^h	5 (1.0)	2 (0.4)	7 (1.4)	6 (2.4)	0 (0)	6 (2.4)
Vascular disorders ⁱ	1 (0.2)	0 (0)	1 (0.2)	2 (0.8)	1 (0.4)	3 (1.2)
Total	17 (3.4)	10 (2.0)	27 (5.4)	17 (6.9)	2 (0.8)	19 (7.7)

- a. eribulin: febrile neutropenia resulting in death (pt 11011003)
TPC: febrile neutropenia (pt 23021006)
- b. eribulin: 3 general health deterioration (pts 11021006, 14011007, 14091003) 1 multiorgan failure due to progressive disease (pt 28271002, died 113 days after treatment discontinuation)
TPC: general worsening of condition (pts 17041002, 30051018);
asthenia due to clinical progression pt 17061003)
- c. TPC: 12021005: liver failure in a patient on hormonal therapy
- d. eribulin: Febrile neutropenia, septic shock (pt 11031004); non-neutropenic sepsis, renal failure (pt 29051004); pulmonary infection (pts 20081016 and 25021012)
TPC: pneumonia (pt 16011002); invasive aspergillosis (pt 14051020)
- e. eribulin: diabetic ketoacidosis (pt 20081009)
- f. eribulin: progressive/metastatic disease (pts 15091002, 24131004, 19041005, 18071001, 14021022)
TPC: progression/metastatic disease (24131005, 20081032; 29021001); abdominal pain due to liver nodule (pt 29021001)
- g. eribulin: depressed LOC due to disease progression (pt 23021001); leptomenigeal disease (pt 23021005); paraplegia (pt 14011018); lower paraparesis (pt 19031011);
- h. eribulin: pulmonary embolism (pt 20081031); lung metastases (pt 30021004); dyspnea/worsening hepatic mets (pt 28241001); dyspnea (pt 23031002); tumor-related respiratory failure (pt 22051004); respiratory failure (pt 17041001); dyspnea/progressive disease (pt 24091005)
TPC: pleural effusion (pt 28281001); pulmonary embolism (pt 13021004); progressive shortness of breath (pt 28011001); respiratory insufficiency (pt 17031003); dyspnea (pts 24021001 and 17061010)

- i. eribulin: cardiovascular insufficiency due to disease progression; patient had history of angina, ischemic heart disease, and hypertension (pt 19111001)
TPC: cardiovascular insufficiency due to disease progression (pt 19061016); embolism (pt 22051002); global hemodynamic failure (pt 11021004)

This reviewer conducted an analysis of deaths attributed to progressive disease within 30 days of drug therapy to determine if there was a discrepancy in the proportion of deaths attributed to progressive disease between the treatment arms and to investigate if there was investigator bias to attribute deaths to progressive disease rather than drug-associated toxicity in the eribulin group.

Table 43 illustrates that a higher percentage of patient deaths occurring within thirty days of therapy were attributed to progressive disease in the control group; fifty-five percent of deaths occurring within 30 days of eribulin therapy were attributed to progressive disease, compared to 68% of deaths in the control group.

Table 44 lists Grade 3, 4 or severe adverse events experienced by patients who died within 30 days of eribulin treatment due to progressive disease. This analysis failed to identify eribulin-treated patients whose deaths were inappropriately attributed to progressive disease. Patient 19111001 had pre-existing cardiac conditions (angina, ischemic heart disease and hypertension) which predisposed her to cardiovascular compromise. Patient 23021005 had leptomeningeal metastases causing decreased level of consciousness; this decreased level of consciousness was likely to be a predisposing factor to the development of pneumonia one day prior to her death, seventeen days after the initial dose of study medication was administered. For patient 28241001, death was attributed to progressive disease, but the investigator also reported that the fatal adverse event dyspnea was possibly related to eribulin. Patient 20021002 died 2 days after hospitalization for a confusional state, 5 days after the Cycle 1, Day 1 dose. A CT scan revealed multiple metastatic cerebral lesions. Neutropenia and hyponatremia (122 mmol/L) were also noted. *It is possible that the hyponatremia experienced by this patient, which may have contributed to this patient's confusional state, could have been related to eribulin administration; however, in this reviewer's opinion, it is more likely that progressive disease was the ultimate cause of this patient's death.*

Table 43: Analysis of Deaths Attributed to Progressive Disease by Treatment Arm

Cause of Death	Number of Deaths within 30 days of study therapy	Eribulin		TPC	
		n	%	n	%
Other	15	9	45.0	6	31.6
Progressive disease	24	11	55.0	13	68.4

Table 44: Tabular Listing of Grade 3, 4 or Severe Adverse Events Reported in Patients Whose Death Occurred Within 30 Days of Therapy and Was Attributed to Progressive Disease

Patient	TTE-Death/ Treatment	TTE- Death/ AE	PT	CTCAE Grade/ Severity	AE Outcome
14011007	24	16	General physical health deterioration	Severe.	Not recovered/not resolved
14011007	24	24	Asthenia	3	Not recovered/not resolved
14011007	24	22	Parotitis	3	Recovered/resolved
14011007	24	15	Pulmonary embolism	3	Not recovered/not resolved
14011007	24	0	General physical health deterioration	5	Fatal
15091002	16	8	Metastases to meninges	Severe	Not recovered/not resolved
15091002	16	8	Fatigue	4	Not recovered/not resolved
15091002	16	0	Metastases to meninges	5	Fatal
19111001	23	0	Cardiovascular insufficiency	5	Fatal
20021002	7	2	Confusional state	Severe	Not recovered/not resolved
23021005	17	13	Metastases to meninges	Severe	Not recovered/not resolved
23021005	17	13	Back pain	3	Not recovered/not resolved
23021005	17	10	Hypertension	3	Not recovered/not resolved
23021005	17	0	Neutropenia	3	Not recovered/not resolved
23021005	17	8	Neutrophil count decreased	3	Recovered/resolved
23021005	17	1	Pneumonia	3	Not recovered/not resolved
23021005	17	5	Somnolence	3	Not recovered/not resolved
23021005	17	1	Somnolence	4	Not recovered/not resolved
23021005	17	0	Meningeal disorder	5	Fatal
24131004	16	9	Dyspnea	3	Recovered/resolved
28241001	15	15	Dehydration	3	Not recovered/not resolved
28241001	15	15	Dyspnea	3	Not recovered/not resolved
28241001	15	10	Neutropenia	4	Recovered/resolved
28241001	15	0	Dyspnea	5	Fatal
28241003	30	9	Abdominal pain upper	3	Not recovered/not resolved

Reviewer Conclusions Regarding Deaths in Study 305

In Study 305, deaths within 30 and 60 days of therapy were relatively infrequent, in light of the severity of the underlying disease of patients enrolled in this study. Furthermore, a smaller percentage of eribulin-treated patients died within 30 days of therapy compared to patients in the control group. The majority of deaths in both treatment arms were attributed to progressive disease, and it appears that attribution of deaths to progressive disease was unbiased and accurate. Drug-related toxicities causing death were primarily related to infection in both treatment groups. Neutropenia and severe infections are well recognized sequelae of cytotoxic chemotherapy drugs used to treat patients with

advanced cancer. Oncologists are trained to treat infections and adequately consent their patients as to the risks of chemotherapy. The Warnings and Precautions section of the label informs physicians of neutropenia and the Adverse Reactions section of the label contains additional information regarding the complications of febrile neutropenia in study 305.

Pooled Analysis of Deaths

Among the 827 patients with advanced breast cancer who were treated with the proposed dose of eribulin in Studies 305, 211 and 201, 4.7% died within 30 days of the last dose or within 30 days of study termination, whichever was longest. Of these, 6 deaths (0.7%) were considered to be at least possibly related to treatment. Table 45 provides a tabular listing of deaths not related to disease progression that were associated with treatment-emergent adverse events in studies 201 and 211. The shaded entry highlights a patient death that was considered not related to eribulin by the investigator, but is considered possibly related to eribulin by this reviewer.

Table 45: Tabular Listing of Deaths Associated With Treatment-Emergent Adverse Events in Studies 201 and 211

Patient Number	Age	Preferred Term	Toxicity Grade	Relationship to Study Drug	Study Drug Action Taken
Study 201^a					
006003	50	Respiratory failure	5	Not related	Withdrawn
0580006	75	Neutropenic Sepsis/thrombocytopenia	5/3	Probably related	None
068007	60	Pyrexia	2	Not related ^b	None
Study 211					
00520102	58	Respiratory failure	5	Not related	None
00570211	67	Respiratory failure	5	Not related	Withdrawn
04680502 ^c	56	Death	5	Possibly related	Withdrawn
04280705 ^d	59	Cardiac arrest	5	Not related	None
04640803	38	Pleural effusion	5	Not related	None
03030901	62	Cerebrovascular accident	5	Not related	Withdrawn

^a. These patients received eribulin at a dose of 1.4 mg/m² on days 1, 8 and 15 of a 28-day cycle, which is not the dose proposed in the label.

^b. Patient 068007 experienced “meningitis listeria” and pyrexia eight days following receipt of Cycle 4, Day 15 therapy. Patient died 35 days later due to meningitis. *There is a reasonable possibility that meningitis was due to immunosuppression caused by eribulin therapy.*

^c. Patient 04680502 died unexpectedly of unknown causes five days after receiving her Cycle 2, Day 1 dose. Laboratory values were normal on the day of therapy, and the only EKG performed was at baseline (sinus tachycardia). An autopsy was not performed.

^d. Patient experienced cardiac arrest 26 days after her last eribulin dose. The patient had discontinued study therapy due to progressive disease 18 days prior to this event. Concurrent conditions at the time of death included pleural effusion and lymphangitis, for which the patient received dexamethasone, oxygen, amiloride/furosemide and prednisolone. The cause of death per the investigator was "carcinomatosis."

Conclusion regarding pooled analysis of deaths

The percentage of deaths occurring within 30 days of therapy for all breast cancer patients treated at the proposed dosage was low, and consistent with that observed in Study 305. Two patients in Study 201 died of infection-related complications that were probably related to eribulin-induced immunosuppression; however, these patients were treated with a more intense dosage regimen compared to eribulin-treated patients in study 305. Additionally, one patient enrolled in Study 211 died suddenly of unknown causes, and there is insufficient information to determine whether this death was related to eribulin.

7.3.2 Serious Adverse Events (SAEs)

Study 305

Adverse events were designated Serious Adverse Events (SAEs) if they met one of the following criteria:

- resulted in death
- was life-threatening (an event in which the subject was at risk of death at the time of the event)
- required inpatient hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability or incapacity
- was a congenital anomaly or birth defect

This definition of SAE is in accordance with ICH E6 Good Clinical Practice Guidelines. SAEs, regardless of causality assessment, were collected for 30 days following study drug discontinuation and through the termination visit, whichever was longer. Serious adverse events that were judged by the investigator to be related to study treatment were to be reported to the sponsor, regardless of the length of time that passed since study treatment completion.

A total of 126 (25%) eribulin-treated patients and 64 (26%) patients in the TPC group experienced a total of 325 treatment emergent SAEs. In general, the per patient incidence of SAEs per MedDRA SOC were comparable. The largest difference between the treatment groups was in the Blood and Lymphatic System Disorders Class; in which 6% of eribulin-treated patients experienced an SAE compared to 2% of patients in the TPC group. Table 46 summarizes the per-patient incidence of SAEs by SOC for each

treatment arm, and Table 47 summarizes the per-patient incidence of SAEs by preferred term.

Table 46: SAE Incidence by MedDRA SOC and Treatment Arm (per patient analysis) – Study 305

SOC	Eribulin N=503 n (%)	TPC N=247 n (%)
Blood and lymphatic system disorders	31 (6)	5 (2)
Respiratory, thoracic and mediastinal disorders	24 (5)	20 (8)
General disorders and administration site conditions	21 (4)	15 (6)
Infections and infestations	21 (4)	7 (3)
Gastrointestinal disorders	17 (3)	12 (5)
Metabolism and nutrition disorders	12 (2)	6 (2)
Nervous system disorders	12 (2)	6 (2)
Musculoskeletal and connective tissue disorders	11 (2)	4 (2)
Neoplasms benign, malignant and unspecified	9 (2)	6 (2)
Vascular disorders	5 (1)	4 (2)
Injury, poisoning and procedural complications	4 (1)	3 (1)
Psychiatric disorders	4 (1)	1 (0)
Skin and subcutaneous tissue disorders	3 (1)	1 (0)
Cardiac disorders	3 (1)	0 (0)
Renal and urinary disorders	2 (0)	3 (1)
Hepatobiliary disorders	2 (0)	2 (1)
Investigations	2 (0)	1 (0)
Immune system disorders	2 (0)	0 (0)
Ear and labyrinth disorders	1 (0)	0 (0)
Reproductive system and breast disorders	1 (0)	0 (0)

Table 47: SAEs by Preferred Term with a Per Patient Incidence \geq 1% by Arm in Study 305

PT	Eribulin N=503 n (%)	TPC N=247 n (%)
Febrile neutropenia	21 (4)	3 (1)
Neutropenia	9 (2)	0 (0)
Dyspnea	7 (1)	9 (4)
Hypercalcemia	7 (1)	2 (1)
Nausea	7 (1)	3 (1)
Pleural effusion	6 (1)	4 (2)
Pulmonary embolism	7 (1)	3 (1)
Pyrexia	7 (1)	2 (1)

PT	Eribulin N=503 n (%)	TPC N=247 n (%)
Asthenia	6 (1)	5 (2)
General physical health deterioration	6 (1)	2 (1)
Malignant neoplasm progression	6 (1)	2 (1)
Vomiting	5 (1)	3 (1)
Pneumonia	4 (1)	2 (1)
Back Pain	3 (1)	4 (2)
Dehydration	3 (1)	2 (1)
Bone Pain	3(1)	0 (0)
Deep vein thrombosis	2 (0)	2 (1)
Respiratory Failure	2 (0)	2(1)
Abdominal pain	1 (0)	4 (2)
Anemia	1(0)	3 (1)
Ascites	1 (0)	2 (1)
Headache	1 (0)	2 (1)
Pain	1 (0)	2 (1)
Renal Failure	1 (0)	2 (1)
Diarrhea	0 (0)	4 (2)
Performance status decreased	0 (0)	3 (1)
Cancer Pain	0 (0)	2 (1)

Blood and Lymphatic System Disorders

The most commonly reported SAEs were related to blood and lymphatic system disorders, which occurred in 6% of patients in the eribulin group. A total of 21 eribulin-treated patients experienced 23 SAEs of febrile neutropenia, 9 patients experienced neutropenia, and one patient each experienced anemia and pancytopenia. As discussed in section 7.3.1, two patients developed febrile neutropenia and fatal infections which resulted in death (patients 11011003 and 25021012); one patient developed *Bacteroides fragilis* bronchopneumonia and the other patient died of septic shock.

Respiratory, Thoracic and Mediastinal Disorders

A total of 24 eribulin-treated patients [5% (versus 8% in the TPC group)] experienced 29 SAEs in the respiratory, thoracic and mediastinal disorders SOC. The most common adverse events in this SOC were pulmonary embolism and dyspnea which were experience by 7 patients each.

One patient (20081031) died due to pulmonary embolism, but the adverse event was considered by the investigator to be unrelated (the patient had fallen and fractured her femur one month prior to the event). Three patients developed non-fatal pulmonary

emboli and one patient developed a pulmonary artery thrombosis; all were considered possibly related to eribulin:

- Patient 14011007 developed a pulmonary embolism, which was noted on a routine CT scan. The patient had multiple bone metastases and had been hospitalized one week earlier for hip pain.
- Patient 22051001 developed a life-threatening pulmonary embolus during hospitalization for vomiting and dehydration.
- Patient 24021002 developed a deep vein thrombosis 7 days after the Cycle 2, Day 1 dose. One week later, a non-fatal pulmonary embolism was identified.
- Patient 19061025 developed a pulmonary artery thrombosis associated with pleuritis, disease progression, and deterioration of her condition with reduction in mobility.

Comment: all but one case of thrombosis occurred in patients who were either hospitalized for other conditions prior to or during detection of the event or were associated with reduction in mobility. There is not enough evidence at this time to declare an association between deep vein thrombosis or pulmonary emboli with eribulin at this time.

7 patients experienced dyspnea, three of which resulted in death.

- Patient 23031002 was a 69 year old woman with chronic obstructive pulmonary disease. Dyspnea, considered by the investigator to be unrelated, was reported 11 days following the Cycle 4, Day 1 dose. The patient was hospitalized and died two weeks later.
- Patient 28241001 was a 60 year old woman with brain metastases who developed Grade 3 dyspnea, considered possibly related by the investigator, on the same day as the Cycle 1, Day 8 dose. CT scans demonstrated worsening hepatic metastases, and the patient was taken off study and transferred to hospice. She died 2 weeks later.
- Patient 30021004 was a 53 year old woman with prior history of asthma, cardiac arrhythmia, and dyspnea, who developed worsening (Grade 3) dyspnea 11 days after the Cycle 1, Day 8 dose. This adverse event was considered possibly related to eribulin by the investigator. The patient died one day later.

Four patients experience non-fatal dyspnea:

- A 72 year old woman developed dyspnea associated with febrile neutropenia, pneumonia, lymphangiosis carcinomatosa and a pleural infection due to *Enterobacter aerogenes*. The pneumonia resolved, but lymphangiosis carcinomatosa and dyspnea were ongoing at the time of her death.
- Two episodes of dyspnea were reported in a 59 year old patient. One episode resolved with empiric therapy for bronchopneumonia and one episode resolved after three weeks.

- One 67 year old patient developed dyspnea associated with a pleural effusion that resolved following pleurocentesis.
- One 53 year old female experienced two episodes of dyspnea; one episode, associated with pneumonia, resolved with antibiotic therapy. The other episode occurred in association with bilateral pleural effusions, lymphangitis, and pneumonia. The patient discontinued study therapy due to progressive disease and was discharged to hospice care.

Comment: Dyspnea occurred in conjunction with other pre-disposing conditions; therefore, there is insufficient evidence to declare an association between dyspnea and eribulin.

Two patients developed respiratory failure that resulted in death and were not considered treatment related:

- Patient 17041001 developed respiratory failure with pleural effusion 23 days after the Cycle 2, Day 8 dose.
- A 38 year old woman with a history of prior pulmonary embolism was hospitalized with panic attacks, fear of breathlessness and dyspnea one week after her Cycle 3, Day 8 dose. Symptoms were attributed to progressive disease. The patient decided she did not want further therapy after receiving one more cycle of eribulin and died two weeks later of respiratory failure.

In addition, 6 patients developed pleural effusions, which were considered unrelated to study therapy.

General Disorders and Administrative Site Conditions

Twenty-one eribulin-treated (4% versus 6% in the TPC group) patients experienced twenty-five SAEs in the general disorders and administrative site conditions SOC. The most common SAEs within this SOC were fatigue or asthenia, which were experienced by eight patients. Seven patients experienced pyrexia. In addition, six patients experienced general health deterioration, which was considered not related to eribulin therapy but was fatal in the following two patients:

- Patient 11021006 developed general physical health deterioration associated with urinary incontinence, somnolence, and food intolerance. Eleven days after the Cycle 8, Day 1 eribulin dose. The patient received palliative care at home and subsequently died 34 days after her last eribulin dose.
- Patient 14011007 experienced general health deterioration 8 days after her cycle 3, day 8 dose. The patient had recently been discharged following hospitalization for fever and parotitis, and hip pain secondary to multiple metastases.

Comment: There appears to be an association between eribulin therapy and fatigue/asthenia and pyrexia. As described in the proposed label, fatigue/asthenia of any grade occurred in 54% of eribulin-treated patients, compared to 40% in the TPC group. The per-patient incidence of Grade 3 and higher fatigue/asthenia was comparable in the two groups (10% in the eribulin group and 11% in the TPC group). Pyrexia was also more common in the eribulin group; pyrexia was reported in 21% of patients who were treated with eribulin, compared to 13% of TPC patients. However, the episodes of general health deterioration occurred in conjunction with advanced disease. Due to the presence of this confounding factor, there is not enough information to declare a causal relationship between eribulin therapy and general health deterioration.

The remaining SAEs, experienced by one patient each, were mucosal inflammation, pain, non-cardiac chest pain, and chills, resulted in hospitalization.

Infections and Infestations

24 SAEs in the infections and infestations SOC were reported in 21 patients treated with eribulin. The infectious events were often, but not always, associated with neutropenia. Three patients died due to infections: patient 20081016 developed a fatal lung infection, patient 29051004 died of sepsis, and 25021012 developed fatal bronchopneumonia (these patients are described in Section 7.3.1. The most common site of infection was the lung, with 7 patients developing either a lung infection, pneumonia, or bronchopneumonia). *Bacteroides fragilis* and *Enterobacter aerogenes* were implicated in 2 patients. Four patients developed catheter-related infections, and cellulitis, erysipelas, and urinary tract infections were reported in two patients each. One patient (24131002) was hospitalized twice for neutropenic sepsis; one episode was associated with an *E. Coli* urinary tract infection (the urinary tract infection was not documented as an SAE, although she was hospitalized). Finally, parotitis, Herpes Zoster, *C. difficile* colitis, and septic shock were reported in one patient each.

Comment: There is a clear association between eribulin therapy and neutropenia, which predisposes patients to serious infections. This information is described in the Warnings and Precautions and Adverse Reactions sections of the proposed label.

Gastrointestinal Disorders

Seventeen eribulin-treated patients experienced 24 SAEs in the gastrointestinal disorders SOC (3% in the eribulin group versus 5% in the TPC group). None of the gastrointestinal SAEs were fatal. 12 patients were hospitalized for nausea or vomiting. One patient with peritoneal and omental metastases had two episodes of bowel obstruction, and 2 patients developed stomatitis. Abdominal pain, ascites, constipation, mouth hemorrhage, esophageal stenosis, esophageal varices, pancreatitis, and rectal hemorrhage were reported once.

Comment: All SAEs other than stomatitis, nausea, vomiting, and constipation occurred in a single patient. Therefore, there is insufficient evidence to declare a causal association

between eribulin and the SAEs of ascites, mouth hemorrhage, esophageal stenosis, esophageal varices, pancreatitis, and rectal hemorrhage. Nausea, vomiting, constipation, and stomatitis occurred in at least 5% of eribulin-treated patients. There is a reasonable likelihood that these adverse reactions are caused by eribulin and therefore these adverse reactions are included in the proposed label (stomatitis is described as mucosal inflammation).

Metabolism and Nutrition Disorders

12 eribulin-treated patients experienced 14 SAEs in the Metabolism and Nutrition Disorders SOC. Hypercalcemia and dehydration were reported in 7 and 3 patients, respectively. Hyperglycemia was experienced in a patient receiving dexamethasone. Hypovolemia was experienced by one patient who had nausea and vomiting. Finally, one 71 year old patient (20081009) with Type 2 diabetes and diabetic retinopathy died due to complications from diabetic ketoacidosis 5 days after the Cycle 1, Day 8 dose.

Comment: These SAEs were rare and occurred in the context of co-morbid conditions or medications that may have caused these adverse events. Therefore, there is insufficient information to declare a causal relationship between eribulin and these adverse events.

Nervous System Disorders

14 SAEs in the Nervous System Disorders SOC were reported for 12 eribulin-treated patients. Two SAEs resulted in death, but were considered unrelated to eribulin by the investigator: Patient 23021005 developed a meningeal disorder due to documented meningeal metastases, and Patient 19031011 developed paraparesis that was considered to be related to clinical progression 16 days after the Cycle 9, Day 1 dose. Two patients experienced epilepsy and a convulsion was reported in one patient; all had brain metastases. Lethargy was reported in two patients, and dizziness, headache, epiduritis, peripheral motor neuropathy, paresthesia, and memory impairment were reported in one patient each.

Comment: Based upon the incidence of peripheral neuropathy in eribulin-treated patients, the temporal association between eribulin administration and emergence of signs and symptoms of peripheral neuropathy, and the known neurotoxicity profile of drugs with similar mechanisms of action, there is adequate evidence of the association of peripheral neuropathy and eribulin. The other SAEs (paraparesis, convulsions, lethargy, and memory impairment) occurred in patients with other predisposing conditions including hepatic metastases.

Musculoskeletal and Connective Tissue Disorders

Twelve musculoskeletal-related SAEs were reported in eleven eribulin-treated patients. None were fatal, nor were they considered to be related to eribulin by investigators. Back pain (3 patients), bone pain (3 patients), muscular weakness (2 patients), musculoskeletal pain (2 patients), pathologic fracture (1 patient), and a tumor-associated fistula (1 patient) were reported.

Neoplasms benign, malignant and unspecified

A total of 9 eribulin-treated patients experienced SAEs in this SOC; 8 SAEs represented disease progression, and were documented as either malignant neoplasm progression or metastases. One ovarian neoplasm was reported, which was determined to be a breast cancer metastasis by biopsy.

Vascular system disorders

A total of 5 SAEs were reported for the vascular system disorder SOC among eribulin-treated patients. Three of the events were venous thrombi and one pulmonary embolus was recorded. In addition, one case of fatal cardiovascular insufficiency in a 61 year old female (patient 19111001) with a history of heart disease and hypertension was reported (see Section 7.3.1 for more details). (Also refer the discussion of SAEs of pulmonary emboli in the Respiratory, Thoracic and Mediastinal Disorders SOC above).

Injuries, Poisonings and Procedural Complications

Bone fractures were reported in three eribulin-treated patients with metastatic disease. In addition, a 69-year-old patient with multiple metastases and a history of polyradiculoneuropathy fell 7 days after the first eribulin dose. She had reported difficulty walking and multiple falls one day after receiving eribulin. The patient received 6 cycles of therapy and did not require another hospitalization for falling.

Psychiatric disorders

Four SAEs were reported in the psychiatric disorders SOC; none were considered related to eribulin by the investigator. Two elderly patients suffered brief confusional states within a week of the first eribulin dose; one patient was subsequently diagnosed with multiple metastatic lesions and terminated participation in the study, and the other patient's confusion subsided with pain medication adjustment. One 70-year old diabetic patient developed a brief change in mental status associated with hypoglycemia secondary to insulin therapy. Finally, a patient with a prior history of panic disorder experienced anxiety while receiving eribulin therapy.

Skin and subcutaneous tissue disorders

Three SAEs relating to skin and subcutaneous tissue disorders were reported in study 305. One patient developed facial angioedema without respiratory compromise 21 hours after administration of her first dose of eribulin; the patient received 2 additional doses without recurrence of this SAE. The second patient developed a rash accompanied by febrile neutropenia 8 days after the Cycle 1, Day 8 dose. The patient received 4 additional cycles without recurrence of the rash. The third patient developed palmar-plantar erythrodysesthesia syndrome accompanied by pancytopenia and stomatitis that required hospitalization and resulted in cessation of therapy.

Cardiac disorders

Three eribulin-treated patients experienced SAEs in the cardiac SOC. Pericardial effusions were reported in two patients; neither resulted in cessation of therapy. One patient had a prior history of pericardial effusion and pericardial tamponade. Cardiac failure occurred in a 76 year old woman with a prior history of hypertension and cardiac disease who had recently withdrawn from the study due to disease progression.

Renal and urinary disorders

One patient who had completed nine cycles of therapy and had recently withdrawn from the study due to progressive disease developed obstructive uropathy. In addition, a 68 year old woman developed Grade 3 acute renal failure 15 days following the Cycle 3, Day 8 dose. The event resolved and the patient received 8 additional cycles at a reduced dose of 1.1 mg/m² until withdrawal due to progressive disease.

Hepatobiliary disorders

One patient with liver metastasis developed hepatitis with increased alanine aminotransferase and aspartate aminotransferase levels 10 times above the upper limit of normal six days after the first eribulin dose. The event resolved within 10 days, and the patient received 19 additional cycles of therapy without hepatitis recurrence. Another patient developed Grade 2 reversible bile duct obstruction associated with a liver metastasis.

Investigations

One patient was hospitalized for a swollen, painful left arm in association with Grade 1 body temperature elevation and the patient subsequently withdrew from study due to progressive disease. Another patient with baseline Grade 2 creatinine elevation developed transient Grade 3 creatinine elevation on Cycle 1 Day 15; creatinine normalized and the patient received 6 additional cycles of eribulin.

Immune system disorders

Hypersensitivity reactions were reported in two patients. One patient with mild asthma developed facial flushing and wheezing after receiving 1 ml of eribulin. Symptoms resolved after receipt of hydrocortisone and nebulization therapy. She received two additional doses with steroid premedication without incident, but subsequently withdrew due to steroid-induced hyperglycemia. Another patient developed itching and swallowing difficulty eight minutes after receipt of the first dose of eribulin. Symptoms resolved with diphenhydramine administration, and the patient received three additional doses (with premedication) without incident.

Comment: Although premedication prior to eribulin infusion was not required or recommended in the Study 305 protocol, thirty-eight percent of eribulin-treated patients received dexamethasone at least once during Study 305. With this caveat in mind, the incidence of hypersensitivity reactions appears low, and the patients described above were able to continue to receive additional eribulin therapy. The applicant proposed to

insert the following language into the Dosage and Administration Section of the label:

(b) (4)

.” The review team recommended taking this statement out of the label because it was potentially promotional and did not provide useful information to health care providers. In addition, the applicant proposed to

(b) (4)

. The review team recommended removing this contraindication from the proposed label because patients who exhibited signs of hypersensitivity did not discontinue eribulin in study 305.

Ear and labyrinth disorders

One 59-year-old patient with a history of Raynaud’s syndrome developed two episodes of vertigo.

Reproductive system and breast disorders

A 49-year-old woman was diagnosed with primary ovarian adenocarcinoma 5 days after the Cycle 16, Day 8 dose of eribulin.

Table 48 compares the per patient incidence of serious adverse events by preferred term in the eribulin group to those in the TPC group as a whole. This table also provides a comparison of SAEs experienced with eribulin to those reported for each major type chemotherapy administered in the TPC group. The two shaded entries (febrile neutropenia and neutropenia) represent the adverse events that occurred in at least 1% of eribulin-treated patients and also occurred substantially more often in the eribulin group compared to the TPC group.

Table 48: Per Patient Incidence of Serious Adverse Events in the Eribulin, TPC and TPC Subgroups

Serious Adverse Events by PT (Per Patient Analysis)	Eribulin % (N = 503)	TPC % (N = 247)	Vinorelbine % (N = 61)	Gemcitabine % (N = 46)	Capecitabine % (N = 44)	Taxanes % (N = 38)	Anthracyclines % (N = 24)
Febrile neutropenia	4.17	1.21	0.00	2.17	0.00	0.00	4.17
Neutropenia	1.79	0.00	0.00	0.00	0.00	0.00	0.00
Dyspnoea	1.39	3.64	4.92	6.52	0.00	2.63	0.00
Hypercalcemia	1.39	0.81	1.64	0.00	0.00	0.00	0.00
Nausea	1.39	0.81	1.64	0.00	0.00	0.00	4.17
Pulmonary embolism	1.39	1.21	1.64	2.17	0.00	0.00	4.17
Pyrexia	1.39	0.81	1.64	0.00	2.27	0.00	0.00
Asthenia	1.19	2.02	0.00	4.35	4.55	2.63	0.00
General physical health deterioration	1.19	0.81	0.00	0.00	4.55	0.00	0.00

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NDA 201532
Eribulin mesylate/Halaven

Serious Adverse Events by PT (Per Patient Analysis)	Eribulin % (N = 503)	TPC % (N = 247)	Vinorelbine % (N = 61)	Gemcitabine % (N = 46)	Capecitabine % (N = 44)	Taxanes % (N = 38)	Anthracyclines % (N = 24)
Pleural effusion	1.19	1.62	1.64	0.00	0.00	2.63	4.17
Malignant neoplasm progression	0.99	0.81	3.28	0.00	0.00	0.00	0.00
Vomiting	0.99	0.40	0.00	0.00	0.00	0.00	0.00
Pneumonia	0.80	0.40	0.00	0.00	2.27	0.00	0.00
Back pain	0.60	1.21	1.64	0.00	2.27	0.00	0.00
Bone pain	0.60	0.00	0.00	0.00	0.00	0.00	0.00
Dehydration	0.60	0.81	1.64	0.00	0.00	0.00	0.00
Catheter related infection	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Confusional state	0.40	0.40	1.64	0.00	0.00	0.00	0.00
Deep vein thrombosis	0.40	0.81	1.64	0.00	0.00	2.63	0.00
Epilepsy	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Erysipelas	0.40	0.40	0.00	2.17	0.00	0.00	0.00
Hypersensitivity	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Lethargy	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Lung infection	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Metastases to meninges	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Muscular weakness	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Musculoskeletal pain	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Pericardial effusion	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Respiratory failure	0.40	0.81	0.00	2.17	0.00	2.63	0.00
Stomatitis	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Urinary tract infection	0.40	0.00	0.00	0.00	0.00	0.00	0.00
Abdominal pain	0.20	1.21	1.64	2.17	2.27	0.00	0.00
Anemia	0.20	0.81	0.00	2.17	0.00	2.63	0.00
Angioedema	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Anxiety	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Ascites	0.20	0.81	0.00	0.00	0.00	5.26	0.00
Bile duct obstruction	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Body temperature increased	0.20	0.40	0.00	0.00	2.27	0.00	0.00
Breast cellulitis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Bronchopneumonia	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Cardiac failure	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Cardiovascular insufficiency	0.20	0.40	0.00	2.17	0.00	0.00	0.00
Catheter site infection	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Cellulitis	0.20	0.40	0.00	0.00	0.00	0.00	0.00

Clinical Review
Martha Donoghue
NDA 201532
Eribulin mesylate/Halaven

Serious Adverse Events by PT (Per Patient Analysis)	Eribulin % (N = 503)	TPC % (N = 247)	Vinorelbine % (N = 61)	Gemcitabine % (N = 46)	Capecitabine % (N = 44)	Taxanes % (N = 38)	Anthracyclines % (N = 24)
Central line infection	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Chills	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Clostridium difficile colitis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Colonic obstruction	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Constipation	0.20	0.40	0.00	2.17	0.00	0.00	0.00
Convulsion	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Cough	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Cytolytic hepatitis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Diabetic ketoacidosis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Dizziness	0.20	0.40	0.00	0.00	0.00	0.00	4.17
Embolism	0.20	0.40	0.00	2.17	0.00	0.00	0.00
Epiduritis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Fall	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Fatigue	0.20	0.40	1.64	0.00	0.00	0.00	0.00
Femur fracture	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Fistula	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Headache	0.20	0.81	1.64	0.00	0.00	2.63	0.00
Herpes zoster	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Hip fracture	0.20	0.40	0.00	0.00	0.00	2.63	0.00
Humerus fracture	0.20	0.40	0.00	0.00	2.27	0.00	0.00
Hyperglycemia	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Hypovolemia	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Intestinal obstruction	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Memory impairment	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Meningeal disorder	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Mental status changes	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Metastases to bone	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Mouth hemorrhage	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Mucosal inflammation	0.20	0.40	0.00	0.00	0.00	0.00	4.17
Neuropathy peripheral	0.20	0.40	1.64	0.00	0.00	0.00	0.00
Neutropenic sepsis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Non-cardiac chest pain	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Obstructive uropathy	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Esophageal stenosis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Esophageal varices hemorrhage	0.20	0.00	0.00	0.00	0.00	0.00	0.00

Serious Adverse Events by PT (Per Patient Analysis)	Eribulin % (N = 503)	TPC % (N = 247)	Vinorelbine % (N = 61)	Gemcitabine % (N = 46)	Capecitabine % (N = 44)	Taxanes % (N = 38)	Anthracyclines % (N = 24)
Ovarian mass	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Ovarian neoplasm	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Pain	0.20	0.81	1.64	0.00	2.27	0.00	0.00
Palmar-plantar erythrodysesthesia syndrome	0.20	0.40	0.00	0.00	0.00	0.00	4.17
Pancreatitis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Pancytopenia	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Paresthesia	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Paraparesis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Parotitis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Pathological fracture	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Peripheral motor neuropathy	0.20	0.40	0.00	0.00	2.27	0.00	0.00
Pharyngolaryngeal pain	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Productive cough	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Pulmonary artery thrombosis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Rash	0.20	0.40	0.00	0.00	0.00	0.00	4.17
Rectal hemorrhage	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Renal failure acute	0.20	0.81	0.00	2.17	2.27	0.00	0.00
Sepsis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Septic shock	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Venous thrombosis	0.20	0.00	0.00	0.00	0.00	0.00	0.00
Vertigo	0.20	0.00	0.00	0.00	0.00	0.00	0.00

Analysis of Serious Adverse Events Occurring in All Breast Cancer Patients Treated With the Proposed Dosage Regimen of Eribulin

The per-patient incidence of serious treatment adverse events in the pooled population of breast cancer patients who received eribulin at the targeted dose was similar to that of study 305.

Table 49 illustrates that the per-patient incidence of SAEs by SOC was similar between the two patient populations. There was no more than a one percent difference in the PPI of SAEs by SOC in the patient populations. The most common SAEs were in the Blood and Lymphatic System Disorders SOC in both groups.

Table 49: Per Patient Incidence of Serious Adverse Events in Study 305 and the Pooled Breast Cancer Population

MeDRA SOC	Study 305 Eribulin-Treated Patients N=503 n (%)	Phase 2/3 Breast Cancer Subjects on Targeted Dose N=827 n (%)
Blood And Lymphatic System Disorders	31 (6)	51 (6)
General Disorders And Administration Site Conditions	21 (4)	44 (5)
Respiratory, Thoracic And Mediastinal Disorders	24 (5)	43 (5)
Infections And Infestations	21 (4)	37 (4)
Gastrointestinal Disorders	17 (3)	30 (4)
Nervous System Disorders	12 (2)	28 (3)
Musculoskeletal And Connective Tissue Disorders	11(2)	21 (3)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	9 (2)	20 (2)
Metabolism And Nutrition Disorders	12 (2)	18 (2)
Injury, Poisoning And Procedural Complications	4(1)	9 (1)
Cardiac Disorders	3 (1)	8 (1)
Psychiatric Disorders	4 (1)	8 (1)
Renal And Urinary Disorders	2 (0)	6 (1)
Vascular Disorders	5(1)	5 (1)
Hepatobiliary Disorders	2 (0)	4 (0)
Skin And Subcutaneous Tissue Disorders	3(1)	4 (0)
Eye Disorders	0 (0)	2 (0)
Immune System Disorders	2 (0)	2 (0)
Investigations	2 (0)	2 (0)
Reproductive System And Breast Disorders	1 (0)	2 (0)
Ear And Labyrinth Disorders	1 (0)	1 (0)

Similarly, the per-patient SAE incidence by preferred term was similar in the study 305 and pooled breast cancer patient populations. Table 50 illustrates that the most common SAEs by preferred term were febrile neutropenia, pyrexia, dyspnea, and neutropenia in the two populations. There was no more than a one percent difference in per-patient incidence of serious adverse events by preferred term in the two patient populations.

Table 50: SAEs by Preferred Term with a Per Patient Incidence $\geq 1\%$ in Either Population

Preferred Term	Eribulin-Treated Patients Study 305 N=503 n (%)	Phase 2/3 Breast Cancer Subjects on Targeted Dose N=827 n (%)
Febrile Neutropenia	21 (4)	32 (4)
Pyrexia	6 (1)	18 (2)
Dyspnea	7 (1)	16 (2)
Neutropenia	9 (2)	16 (2)
Pleural Effusion	6 (1)	14 (2)
Peripheral neuropathy based on broad MedDRA SMQ	6 (1)	10 (1)
Asthenia + Fatigue	6 (1)	9 (1)
Nausea	7 (1)	9 (1)
Vomiting	5 (1)	9 (1)
Hypercalcemia	7 (1)	7 (1)
Pain	1 (0)	7 (1)
Pulmonary Embolism	7 (1)	7 (1)
Back Pain	3 (1)	6 (1)
Abdominal Pain	1 (0)	5 (1)
Bone Pain	3 (1)	5 (1)
Dehydration	3 (1)	5 (1)
General Physical Health Deterioration	6 (1)	5 (1)
Metastases To Meninges	3 (1)	5 (1)
Muscular Weakness	3 (1)	5 (1)
Peripheral Neuropathy (1)	3 (1)	5 (1)
Pneumonia	4 (1)	5 (1)
Malignant neoplasm progression	6 (1)	4 (0)

7.3.3 Dropouts and/or Discontinuations

Study 305

In this analysis, the disposition datasets for Study 305 were analyzed to determine the primary reason for patient discontinuation from study therapy because this analysis appeared to more accurately reflect the reasons for discontinuation. Therefore, the percentages listed in Table 51 and Table 52 are based on the ITT population rather than the safety population. Overall, the reasons for discontinuation from study therapy were similar between the two arms in Study 305 (Table 51). The majority of patients discontinued study treatment due to progressive disease according to RECIST criteria; however, a higher percentage of patients in the eribulin arm discontinued due to progressive disease by RECIST, and a higher percentage of patients on the TPC arm

discontinued therapy due to a clinical diagnosis of progression. The incidence of discontinuation due to adverse events was similar in the two groups.

Table 51: Reasons for Patient Discontinuation in Study 305

Reason for Discontinuation	Eribulin (N = 508)	TPC (N = 254)
Progressive Disease	336 (66)	155 (61)
Adverse Event	56 (11)	25 (10)
Clinical Progression	61 (12)	36 (14)
Physician Decision	14 (3)	12 (5)
Death	3 (1)	2 (1)
Patient Decision	9 (2)	5 (2)
Other	5 (1)	9 (4)

At the time of data cut-off (May 12, 2009), 24 patients on the eribulin arm and 9 patients on the TPC arm remained on therapy.

Table 52 outlines the types of adverse events leading to discontinuation of therapy in Study 305. Although the percentage of patients who discontinued therapy due to adverse events was similar in the two arms, a higher percentage of patients on the eribulin arm discontinued due to neurotoxicity (primarily peripheral neuropathy). Dermatologic toxicities precipitated treatment discontinuation more frequently in the TPC arm.

Table 52: Adverse Events Leading to Discontinuation of Therapy in Study 305

Adverse Event Type	Eribulin N = 508 n (%)	TPC N =254 n (%)
Neurotoxicity	29 (6)	3 (1)
Infections	6 (1)	2 (1)
Asthenia/Fatigue	5 (1)	3 (1)
Elevations in Liver Enzymes/Hepatotoxicity	3 (1)	1 (0)
Thrombotic Event	2 (0)	1 (0)
Other	12 (2)	10 (5)
Dermatologic Toxicity/HFS	0 (0)	5 (2)

The statistics in Table 51 and Table 52 differ slightly from those presented in the Study 305 clinical study report for the following reasons:

Adjustments in reasons for discontinuation in TPC arm:

- Two patients discontinued due to disease progression which was classified by the applicant as an adverse event in the dataset
- Patient 18071003’s discontinuation was classified as “physician decision”, but the patient actually discontinued due to SAEs of decreased performance status and dyspnea.
- Two patients were classified as discontinuing due to “Patient decision”, but review of narratives indicated that they discontinued due to SAEs
 - Patient 3021010 developed Grade 3 fatigue 7 days after the last anthracycline dose, leading to discontinuation of treatment.
 - Patient 28271008 developed grade 3 abdominal discomfort on the last day of vinorelbine therapy

Adjustments in reasons for discontinuation in the eribulin arm:

Table 53 lists patients that were categorized by the applicant as discontinuing therapy due to “Physician decision”, “Other” or “Patient Withdrawal”; however, upon review, it is likely that an adverse event precipitated discontinuation of eribulin therapy in these patients. Table 54 provides a comprehensive listing of patients enrolled in Study 305 that discontinued study therapy for reasons other than disease progression.

Table 53: Eribulin Patients Reclassified As Discontinuing Therapy Due To An Adverse Event in Study 305

Patient	Arm	Reason for Discontinuation	Comments
29051004	E7389	Other	Grade 4 sepsis accompanied by hypotension, hyperglycemia, renal failure after Cycle 2, Day 8 dose. Died one day later.
14051002	E7389	Physician decision	Developed moderate neuropathy after 11 cycles; ongoing for at least 21 months (as of data-cutoff)

Patient	Arm	Reason for Discontinuation	Comments
28011003	E7389	Physician decision	Bone marrow depression & wound from infected venous catheter
24051002	E7389	Physician decision	Grade 2 fatigue reported on Day 1 of Cycle 3 leading to discontinuation of study treatment per narrative
24131002	E7389	Physician decision	Grade 4 peripheral neuropathy reported 7 days after Cycle 4, Day 1 dose – led to discontinuation per narrative; ongoing at time of death.
28081003	E7389	Withdrawal by subject	Hospitalized due to weakness and mouth hemorrhage 2 days after Day 1, Cycle 4 dose prior to withdrawal.

Table 54: Tabular Listing of Patients who Discontinued Eribulin Therapy Due to Adverse Events, “Withdrawal by Subject”, “Physician Decision”, or “Other” in Study 305

Patient ID	Reason for Discontinuation	Additional Explanation form CRFs, Narratives, or Adverse Event Dataset
11021006	Adverse event	Drug discontinued due to general physical health deterioration 11 days after Cycle 1, Day 8 dose.
11061013	Adverse event	Asthenia 6 days after Cycle 8 Day 8 dose.
23031002	Adverse event	Dyspnea developed 11 days after Cycle 4 Day 1 dose, ongoing at time of death and fatal 14 days later.
24041008	Adverse event	Grade 3 ALT elevation 30 days after Cycle 10 Day 1 dose.
26041005	Adverse event	Grade 3 ALT elevation 7 days after Cycle 7 Day 1 dose.
25021009	Adverse event	Fatigue 11 days after Cycle 7, Day 8 dose.

Patient ID	Reason for Discontinuation	Additional Explanation form CRFs, Narratives, or Adverse Event Dataset
26021003	Adverse event	Grade 3 fatigue 1 day after Cycle 15, Day 1 dose; resolved 16 days later.
26021004	Adverse event	Grade 3 Fatigue
17061006	Adverse event	Grade 3 paresthesia developed on Day 8, Cycle 9; ongoing at time of data cut-off (9 months later)
28351002	Adverse event	Grade 3 neuropathy 7 days after Cycle 11, Day 1 dose. Ongoing at time of death, 84 days after last eribulin dose.
28121002	Adverse event	Grade 3 peripheral neuropathy reported 2 days after Cycle 5, Day 1 dose. Resolved after 41 days.
16041007	Adverse event	Grade 2 hepatic enzyme elevation and jaundice developed 11 days after Cycle 6, Day 1 dose. Ongoing at time of death (attributed to disease progression), 49 days after last eribulin dose.
14011017	Adverse event	Weight loss after receiving 6 cycles of eribulin; patient alive at data cut-off.
30111002	Adverse event	CNS metastases. Randomized but did not receive study medication
28271002	Adverse event	SAE Grade 3 peripheral motor neuropathy and peripheral sensory neuropathy reported 7 days after Cycle 2, Day 1; ongoing at time of death (attributed to multi-organ failure due to disease progression), 113 days after last eribulin dose
19111010	Adverse event	Grade 2 peripheral motor neuropathy and peripheral sensory neuropathy noted after Cycle 10, Day 1 dose and Cycle 11, Day 8 dose, respectively. Ongoing at data cut-off, 11 months after discontinuation of eribulin.
24041023	Adverse event	Alopecia, diarrhea, fatigue, "feeling low" and mouth ulcers 6 days after Cycle 1, Day 8 dose.
24041005	Adverse event	Withdrew from study after the Cycle 10, Day 8 eribulin dose due to left lower extremity paresthesias, sensorimotor disorder, hypoesthesia, and neuropathy
28281006	Adverse event	Grade 3 neuropathy reported after Cycle 2, Day 8 dose.
29041007	Adverse event	Grade 3 peripheral motor neuropathy after Cycle 13, Day 8 dose.
29091001	Adverse event	Grade 3 anorexia, asthenia and grade 2 peripheral sensory neuropathy 5 days after Cycle 7, Day 1 dose.

Patient ID	Reason for Discontinuation	Additional Explanation form CRFs, Narratives, or Adverse Event Dataset
14051006	Adverse event	Grade 2 peripheral motor neuropathy and Grade 3 peripheral sensory neuropathy reported on Cycle 6 Day 1 dose; ongoing at time of data cut-off 2 years later.
24081001	Adverse event	Grade 2 neuropathy 10 days after Cycle 5, Day 8 dose; ongoing at time of death, 90 days after the last eribulin dose.
13021003	Adverse event	Grade 2 toxicity of upper and lower extremities
14011003	Adverse event	Grade 3 paresthesia reported Day 8, Cycle 4; ongoing at time of death, 350 days after last eribulin dose.
25071001	Adverse event	Peripheral sensory neuropathy reported 7 days after Cycle 1, Day 8 dose; resolved after 217 days. Withdrew after 6 cycles of eribulin therapy due to neurotoxicity; died due to progressive disease 306 days after last eribulin dose.
13011006	Adverse event	Grade 3 peripheral neuropathy 14 days after Cycle 6, Day 8 dose; resolved after 78 days.
19031015	Adverse event	Grade 4 neutropenia reported 7 days after Cycle 6, day 1 dose) despite earlier dose delay and reduction
13041002	Adverse event	Grade 2 peripheral sensory neuropathy reported on the day of the Cycle 5, Day 1 dose; ongoing at time of death 353 days after her last eribulin dose.
24051001	Adverse event	Withdrew from study 7 days after Cycle 2, Day 1 dose due to diabetes mellitus – “related to dexamethasone” therapy, which was required due to infusion-related hypersensitivity reaction which occurred with first dose.
28271006	Adverse event	Grade 3 peripheral neuropathy 14 days after Cycle 7, Day 8 dose; ongoing at time of data cut-off, 10 months later.
14051013	Adverse event	Grade 3 peripheral neuropathy reported on the day of the Cycle 6, Day 8 dose; ongoing at time of death 375 days after her last eribulin dose.
11061006	Adverse event	Grade1 peripheral sensory neuropathy 27 days after the Cycle 11, Day 1 dose; ongoing at time of data cutoff, 10 months later.
16041008	Adverse event	SAE pneumonia “caused by immunosuppression” 7 days after Cycle 16, Day 8 dose; resolved 17 days later.

Patient ID	Reason for Discontinuation	Additional Explanation form CRFs, Narratives, or Adverse Event Dataset
25021012	Adverse event	Grade 3 aspiration pneumonia, febrile neutropenia, and <i>B. fragilis</i> sepsis 9 days, after Cycle 2, Day 1 dose. Condition deteriorated and died 12 days after last dose.
13021005	Adverse event	Moderate polyneuropathy (no narrative available)
13011012	Adverse event	Grade 2 polyneuropathy reported 21 days after Cycle 8, Day 8 dose; ongoing at time of death, 415 days after her last eribulin dose.
28151016	Adverse event	Grade 2 pulmonary embolism 9 days after last eribulin dose
20081016	Adverse event	Grade 3 pulmonary infection reported 7 days after Cycle 3, Day 8 dose; not neutropenic. Patient worsened and died 4 days later; death attributed to pulmonary infection due to mucositis/aspiration.
14051018	Adverse event	Pyelonephritis reported 10 days after Cycle 3, Day 8 dose.
11061005	Adverse event	Grade 3 peripheral sensory neuropathy reported 20 days after Cycle 11, Day 8 dose; improving 10 months later, at data cut-off
19111009	Adverse event	Grade 2 peripheral sensory neuropathy reported 3 days after Cycle 10, Day 8 dose; ongoing 1 year later.
19111008	Adverse event	Grade 2 peripheral motor neuropathy reported on Day 1 of Cycle 8; ongoing at time of death 245 days after last eribulin dose.
19061010	Adverse event	Grade 3 peripheral motor and sensory neuropathy reported 7 days after Cycle 6 Day 8 dose; ongoing at time of death, 380 days after last eribulin dose.
20091002	Adverse event	Grade 3 peripheral sensory neuropathy reported one day after Cycle 5, Day 1 dose; ongoing at time of data cut-off, 10 months later.
29041006	Adverse event	Grade 3 peripheral sensory neuropathy 14 days after Cycle 7, Day 8 dose; ongoing at time of data cut-off, 10 months later.
11011003	Adverse event	Grade 4 febrile neutropenia, septic shock reported 6 days after Cycle 2, Day 8 dose. Worsened to Grade 5 one day later.
24021002	Adverse event	Grade 3 deep vein thrombosis reported 7 days after the Cycle 3, Day 1 dose. Grade 4 pulmonary embolism reported one week later; pulmonary embolism resolved and Deep vein thrombosis improved at time of death, 209 days after her last dose of eribulin.

Patient ID	Reason for Discontinuation	Additional Explanation form CRFs, Narratives, or Adverse Event Dataset
14081004	Adverse event	Grade 2 “abnormal coordination”, Grade 3 peripheral neuropathy reported 1 day after Cycle 16, Day 8 dose; Grade 4 neutropenia also occurred reported 5 days later. Abnormal coordination and peripheral neuropathy ongoing at time of data cut-off, 9 months later.
19061004	Adverse event	Asthenia reported 14 days after Cycle 6, Day 8 dose. Also experienced leg weakness secondary to spinal metastases.
14021009	Other	Increased Calcium 15.3 mg/dL; (CRF and narrative not available.)
28151020	Other	Grade 3 neutropenia noted at screening; patient did not receive study drug
25011001	Other	Patient decided to end treatment after 8 months of therapy (CRF and narrative not available)
20011006	Other	Patient refused treatment. (CRF and narrative not available)
26041003	Other	Ovarian mass reported 5 days after Cycle 16, Day 8 dose of eribulin. Ovarian adenocarcinoma confirmed after resection.
29051004	Other	PMH Type II DM. Presented with Grade 4 sepsis accompanied by hypotension, hyperglycemia, and renal failure after Cycle 2, Day 8 dose. WBC 16,800/mcL with ANC: 517/mcL. clinical disease progression with skin nodules and larger breast lesion noted on exam. Died one day later.
24041015	Physician decision	Physician decision to stop treatment after 9 cycles of therapy. No information in narrative about reason. Patient alive at data cutoff.
14051002	Physician decision	Developed moderate neuropathy after 11 cycles; ongoing for at least 21 months (as of data-cutoff)
28011003	Physician decision	Physician's decision to stop treatment due to bone marrow depression & wound from infected venous port.
24031015	Physician decision	Disease progression
28031001	Physician decision	Clinical disease progression
14011012	Physician decision	Stable disease
24051002	Physician decision	Grade 2 fatigue reported on Day 1 of Cycle 3

Patient ID	Reason for Discontinuation	Additional Explanation form CRFs, Narratives, or Adverse Event Dataset
14031004	Physician decision	Hepatectomy after 20 cycles of eribulin. Patient had liver metastases.
19011005	Physician decision	"in best interest of the patient" no narrative or CRF available.
24131002	Physician decision	Grade 4 peripheral neuropathy reported 7 days after Cycle 4, Day 1 dose; ongoing at time of death attributed to disease progression, 51 days after the last dose of eribulin
14081013	Physician decision	Physician noted "no benefit with the study treatment"
17051003	Physician decision	Physician noted "not sufficient response"
14041003	Physician decision	"Partial response to study treatment"
20081017	Physician decision	Patient did not receive treatment; physician noted that the patient did not meet key inclusion criteria #2.
14051004	Physician decision	"Pulmonary lesions were stable"
13011010	Physician decision	Stable disease after 8 cycles of therapy
13011015	Physician decision	Stable disease after 8 cycles of therapy
24051003	Physician decision	Treatment discontinued after 15 cycles of therapy based upon re-evaluation of CT scans
*28151013	Physician decision	"Tumor marker increased and target lesion up by 17.8%"
11011011	Withdrawal by subject	Subject withdrew consent after four months of therapy
13041001	Withdrawal by subject	Subject withdrew consent after Cycle 2, Day 1 therapy. Developed Grade 3 pneumonia and Grade 4 neutropenia after Cycle 1, Day 1 dose.
14031005	Withdrawal by subject	Subject withdrew consent
19031001	Withdrawal by subject	Subject withdrew consent; did not receive therapy
19031008	Withdrawal by subject	Subject withdrew consent after one cycle of therapy
19061021	Withdrawal by subject	Subject withdrew consent

Patient ID	Reason for Discontinuation	Additional Explanation form CRFs, Narratives, or Adverse Event Dataset
28071004	Withdrawal by subject	Subject withdrew consent after Cycle 1, Day 8 dose. Developed Grade 3 back pain (associated with disc herniation) 13 days after this dose.
28081003	Withdrawal by subject	Subject withdrew consent; hospitalized due to weakness and mouth hemorrhage 2 days after Day 1, Cycle 4 dose prior to withdrawal.
30011009	Withdrawal by subject	Subject withdrew consent
30031009	Withdrawal by subject	Subject withdrew consent after 5 cycles of therapy

* Randomized to TPC group but treated in eribulin Group; for efficacy analyses, the applicant counts this patient in ITT population for TPC.

7.3.4 Significant Adverse Events

The ICH E3 guidance recommends that marked laboratory abnormalities not meeting the definition of serious adverse events also be considered significant adverse events. These laboratory abnormalities are described in Section 7.4.2 of this review.

In addition, the ICH E3 guidance considers other potentially important abnormalities, such as severe adverse events (i.e., \geq Grade 3 by CTCAE), that do not meet the definition of a severe adverse event potentially significant. A discussion of severe adverse events is included in the common adverse events section of this review.

The following describes a review of the 406 safety database using Standardized MedDRA Queries (SMQs).

Using FDA MAED software, narrow scope MedDRA SMQs were analyzed to look for potential safety signals not identified through analyses of adverse events by MedDRA system organ class, high level term, or preferred term.

Table 55 provides a listing of adverse events identified by narrow scope MedDRA SMQ that occurred in ≥ 1 % of eribulin-treated patients (in descending of incidence).

Table 55: Per Patient Incidence of Adverse Events by Narrow Scope MedDRA SMQ in Study 305

NSMQ	Eribulin (N = 503)			TPC (N = 247)			Eribulin vs. TPC	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value
(1) Hematopoietic cytopenias	1278	290	57.65	307	88	35.63	2.46	<.0001
(2) Leucopenia	1241	289	57.46	281	81	32.79	2.77	<.0001
(1) Peripheral neuropathy	233	132	26.24	44	27	10.93	2.90	<.0001
(1) Malignancies	46	36	7.16	19	14	5.67	1.28	0.5339
(1) Depression and suicide/self-injury	37	29	5.77	3	3	1.21	4.98	0.0032
(1) Agranulocytosis	31	24	4.77	5	4	1.62	3.04	0.0389
(1) Hyperglycemia/new onset diabetes mellitus	43	22	4.37	13	7	2.83	1.57	0.4203
(2) Malignancy related conditions	27	21	4.17	13	9	3.64	1.15	0.8440
(1) Embolic and thrombotic events	19	17	3.38	11	9	3.64	0.93	0.8344
(2) Malignant or unspecified tumors	18	15	2.98	6	5	2.02	1.49	0.6303
(2) Thrombocytopenia	34	15	2.98	26	14	5.67	0.51	0.1048
(2) Embolic and thrombotic events, venous	16	14	2.78	9	7	2.83	0.98	1.0000
(1) Angioedema	9	7	1.39	4	3	1.21	1.15	1.0000

The following types of adverse events are addressed elsewhere in this review: Hematopoietic cytopenias, leucopenia (predominantly neutropenia), peripheral neuropathy, thrombocytopenia, agranulocytosis (which includes sepsis, neutropenia, pancytopenia, and neutropenia-related adverse events), and embolic/thrombotic events.

Angioedema: Four of seven patients identified by narrow scope SMQ had symptoms consistent with hypersensitivity reactions that were classified as serious and required systemic antihistamine or corticosteroid therapy. One patient had a Grade 2 hypersensitivity reaction; one had a moderate hypersensitivity reaction. One patient developed an SAE of Grade 1 angioedema 21 hours after her first eribulin dose, without symptoms of airway obstruction. The angioedema resolved within 2 days of administration of dexamethasone (this patient is also described in Section 7.3.2 of this review under Skin

and Subcutaneous Tissues Disorders). Another patient developed a “moderate rash.” Patients tolerated subsequent therapy with premedication. See Section 7.3.2 for discussion of serious adverse events in the Immune System Disorder and Skin and Subcutaneous Tissue Disorder SOCs.

Four patients experienced non-serious adverse events that were temporally associated with eribulin administration. One patient experienced a Grade 2 hypersensitivity reaction considered possibly related to eribulin by the investigator; therapy was subsequently discontinued. Three patients experienced adverse reactions considered possibly or probably related by the investigator, but continued to receive at least one additional cycle of therapy: One patient had Grade 1 wheezing, one patient experienced a grade 2 hypersensitivity reaction and another patient experienced two Grade 1 hypersensitivity reactions.

Depression and Suicide/Self-injury:

Table 56 presents a comparison of adverse events included in the Depression and Suicide/Self-injury SMQ that were reported in Study 305. A higher percentage of patients experienced depression of any toxicity Grade in the eribulin group. However, the percentage of patients experiencing severe depression was comparable. Of note, a higher percentage of patients had baseline signs and symptoms of depression in the eribulin arm (7.7%), compared to the TPC arm (4.7%). Neither self-injury, suicidal ideation, suicidal behavior, nor suicidal attempt were reported in either treatment group.

Table 56: Adverse events Captured by the Depression and Suicide/Self-injury SMQ in Study 305

MedDRA Preferred Term	Eribulin N=503				TPC N=247			
	All Grades		Grades 3 and above		All Grades		Grades 3 and above	
	n	%	n	%	n	%	n	%
Depression	25	5	3	1	3	1	0	0
Depressed Mood	4	1	0	0	0	0	0	0
Mood Altered	2	0	0	0	0	0	0	0
Alcoholism	1	0	0	0	0	0	0	0
Mood Swings	1	0	0	0	0	0	0	0

Hyperglycemia/new onset diabetes mellitus

Table 57 presents a comparison of adverse events included in the Hyperglycemia/New Onset Diabetes Mellitus SMQ for Study 305. A higher percentage of patients experienced adverse related to aberrations in serum glucose or diabetes in the eribulin group. However, two episodes of diabetes mellitus occurred in patients with a prior history of type 2 diabetes (one of whom died of diabetic ketoacidosis), and the third was steroid-induced.

Table 57: Adverse events Captured by the Hyperglycemia/New Onset Diabetes Mellitus SMQ in Study 305

MedDRA Preferred Term	Eribulin N=503				TPC N=247			
	All Grades		Grades 3 and above		All Grades		Grades 3 and above	
	n	%	n	%	n	%	n	%
Diabetes mellitus	3	1	0	0	1	0	0	0
Diabetic ketoacidosis	1	0	1	0	0	0	0	0
Glucose tolerance impaired	1	0	0	0	0	0	0	0
Hyperglycemia	18	4	6	1	6	2	2	1
Hypoglycemia	0	0	0	0	3	1	0	0

Comment: Glucose was not routinely monitored during study 305, so the incidence of hyperglycemia or hypoglycemia may be underreported in both arms.

Malignancy-related Conditions

The Malignancies SMQ captures adverse events with preferred terms included in the following (narrower scope) SMQs: Malignant or Unspecified Tumors, Malignancy-Related Conditions, and Malignancy Related Therapeutic and Diagnostic Procedures. Table 58 presents a comparison of adverse events included in the Malignancies SMQ for Study 305. The adverse events captured by this SMQ are primarily related to the patients' underlying breast cancer, and the incidences of these adverse events are comparable.

Table 58: Adverse events Captured by the Malignancies SMQ in Study 305

MedDRA Preferred Term	Eribulin N=503				TPC N=247			
	All Grades		Grades 3 and above		All Grades		Grades 3 and above	
	n	%	n	%	n	%	n	%
Brain Cancer Metastatic	0	0	0	0	1	0	1	0
Breast Cancer	1	0	1	0	0	0	0	0
Breast Mass	1	0	0	0	0	0	0	0
Cancer Pain	8	2	1	0	4	2	2	1
Ear Neoplasm	1	0	0	0	0	0	0	0
Hepatic Neoplasm	0	0	0	0	1	0	1	0
Malignant Neoplasm Progression	5	1	3	1	3	1	1	0

MedDRA Preferred Term	Eribulin N=503				TPC N=247			
	All Grades		Grades 3 and above		All Grades		Grades 3 and above	
	n	%	n	%	n	%	n	%
Metastatic Pain	6	1	3	1	1	0	0	0
Ovarian Mass	1	0	1	0	0	0	0	0
Ovarian Neoplasm	1	0	0	0	0	0	0	0
Thyroid Neoplasm	1	0	0	0	0	0	0	0
Tumor Hemorrhage	2	0	0	0	2	1	0	0
Tumor Marker Increased	1	0	0	0	0	0	0	0
Tumor Pain	4	1	0	0	3	1	0	0
Tumor Related Complication	2	0	1	0	0	0	0	0
Tumor Ulceration	1	0	0	0	0	0	0	0

7.3.5 Submission Specific Primary Safety Concerns

Neuropathy

Neuropathy is a primary safety concern with eribulin for several reasons. Neuropathies are commonly associated with other approved microtubule inhibitors. In addition, neuropathies were the most common toxicity associated with discontinuation of eribulin therapy in Study 305. Finally, neuropathies have the potential to impact quality of life. A discussion of serious adverse events and discontinuations relating to neurotoxicity are presented in Sections 7.3.2 and 7.3.3. Among the 503 patients who received eribulin in Study 305 peripheral neuropathy was reported in 181 (36%), and Grade 3 and 4 peripheral neuropathy was reported in 41 (7.8%) and 2 (0.4%), respectively. Peripheral neuropathy SAEs were reported in 3 (0.6%) patients. Fourteen (2.8%) of patients required dose reductions due to peripheral neuropathies, and 27 (5.4%) of patients discontinued eribulin due to neurotoxicity. Peripheral motor neuropathy occurred in 22 (4.4%) patients.

In Study 305, baseline neuropathy of Grade 1 or Grade 2 severity was reported in 87 (17.3%) and 16 (3.2%) patients, respectively. Of the 43 (8.5%) patients who developed Grade 3 or 4 peripheral neuropathy, 13 (2.6%) patients had baseline neuropathy.

The applicant conducted Kaplan-Meier analyses to examine the relationship between the time from initiation of eribulin therapy to development or progression of peripheral neuropathies of Grade 2 or greater severity (Table 59). If patients had baseline neuropathy but did not have a toxicity grade recorded, they were assigned a baseline CTCAE toxicity of 1 or 2. Patients were censored at death, loss to follow-up, or database

cutoff if they had not yet developed a new or worsening peripheral neuropathy. When patients with missing grades were assigned a Grade of 1, 84 (19.1%) of patients experienced a new or worsening peripheral neuropathy during the study, compared to 18 (8.4%) of patients in the TPC arm. Moreover, eribulin-treated patients were at increased risk of developing a new or worsening neuropathy within the first year compared to all patients treated in the TPC arm (21.4% versus 9.5%). The estimate of the one-year development or progression of peripheral neuropathy for eribulin-treated patients was approximately double that of those treated with vinorelbine or capecitabine (Table 60 and Table 61). However, when compared to patients treated with taxanes, the estimate of the one-year development/progression was lower in the eribulin group (21.1% for eribulin group and 25.6% for the taxane group) (Table 62).

Table 59: Applicant-Conducted Analysis of Time to Development of Progression of Peripheral Neuropathy in Study 305 (copied from submission)

		E7389 (N=440)	TPC (N=214)
Treatment of Physician's Choice			
OVERALL			
Number of patients	Peripheral Neuropathy Censored	84 (19.1%) 356 (80.9%)	18 (8.4%) 196 (91.6%)
Kaplan-Meier estimate of TDPPN	1st Quartile (95% CI)	(299.0,)	(,)
	Median (95% CI)	(,)	(,)
	3rd Quartile (95% CI)	(,)	(,)
Kaplan-Meier estimate of TDPPN (1 year)	1-year TDPPN (95% CI)	0.786 (0.744, 0.829)	0.905 (0.862, 0.947)
Kaplan-Meier estimate of TDPPN (2 years)	2-year TDPPN (95% CI)	0.769 (0.721, 0.817)	0.905 (0.862, 0.947)
Hazard ratio (E7389/TPC)*	Estimate (95% CI)	2.309 (1.388, 3.841)	

Patients who had an existing no preexisting peripheral neuropathy (or grade 1) at baseline are considered progressed at a time such that they reach grade 2 or more for any peripheral neuropathy AE terms. Patients who had a grade 2 peripheral neuropathy at baseline are considered progressed at a time where they reach grade 3 or greater peripheral neuropathy. Patients are censored if they die or are lost to follow-up prior to development/progression. Baseline CTC has been set as grade 1 if missing.

Table 60: Applicant-Conducted Kaplan-Meier Estimate of Time to-Development of Progression of Peripheral Neuropathy in Study 305 – Comparison to Vinorelbine Group (copied from submission)

Treatment of Physician's Choice		E7389 (N=118)	TPC (N=62)
VINORELBINE			
Number of patients	Peripheral Neuropathy Censored	20 (16.9%) 98 (83.1%)	5 (8.1%) 57 (91.9%)
Kaplan-Meier estimate of TDPPN	1st Quartile (95% CI) Median (95% CI) 3rd Quartile (95% CI)	(215.0,) (,) (,)	(,) (,) (,)
Kaplan-Meier estimate of TDPPN (1 year)	1-year TDPPN (95% CI)	0.814 (0.739, 0.888)	0.904 (0.819, 0.988)
Kaplan-Meier estimate of TDPPN (2 years)	2-year TDPPN (95% CI)	(0.000,)	0.904 (0.819, 0.988)
Hazard ratio (E7389/TPC)*	Estimate (95% CI)	2.176 (0.816, 5.797)	

Patients who had an existing no preexisting peripheral neuropathy (or grade 1) at baseline are considered progressed at a time such that they reach grade 2 or more for any peripheral neuropathy AE terms. Patients who had a grade 2 peripheral neuropathy at baseline are considered progressed at a time where they reach grade 3 or greater peripheral neuropathy. Patients are censored if they die or are lost to follow-up prior to development/progression. Baseline CTC has been set as grade 1 if missing.

Table 61: Applicant-Conducted Kaplan-Meier Estimate of Time to-Development of Progression of Peripheral Neuropathy in Study 305 – Comparison to Capecitabine Group (copied from submission)

Treatment of Physician's Choice		E7389 (N=77)	TPC (N=44)
CAPECITABINE			
Number of patients	Peripheral Neuropathy Censored	16 (20.8%) 61 (79.2%)	4 (9.1%) 40 (90.9%)
Kaplan-Meier estimate of TDPPN	1st Quartile (95% CI) Median (95% CI) 3rd Quartile (95% CI)	372.0 (187.0,) (,) (,)	(,) (,) (,)
Kaplan-Meier estimate of TDPPN (1 year)	1-year TDPPN (95% CI)	0.772 (0.668, 0.877)	0.890 (0.788, 0.992)
Kaplan-Meier estimate of TDPPN (2 years)	2-year TDPPN (95% CI)	(0.000,)	(0.000,)
Hazard ratio (E7389/TPC)*	Estimate (95% CI)	2.434 (0.813, 7.292)	

Patients who had an existing no preexisting peripheral neuropathy (or grade 1) at baseline are considered progressed at a time such that they reach grade 2 or more for any peripheral neuropathy AE terms. Patients who had a grade 2 peripheral neuropathy at baseline are considered progressed at a time where they reach grade 3 or greater peripheral neuropathy. Patients are censored if they die or are lost to follow-up prior to development/progression. Baseline CTC has been set as grade 1 if missing.

Table 62: Applicant-Conducted Analysis of Time to Development of Progression of Peripheral Neuropathy in Study 305– Comparison to Taxane Group (copied from submission)

		E7389 (N=71)	TPC (N=38)
Treatment of Physician's Choice			
TAXANES			
Number of patients	Peripheral Neuropathy Censored	14 (19.7%) 57 (80.3%)	9 (23.7%) 29 (76.3%)
Kaplan-Meier estimate of TDPPN	1st Quartile (95% CI)	(106.0,)	123.0 (75.0,)
	Median (95% CI)	(,)	(,)
	3rd Quartile (95% CI)	(,)	(,)
Kaplan-Meier estimate of TDPPN (1 year)	1-year TDPPN (95% CI)	0.789 (0.690, 0.888)	0.744 (0.599, 0.889)
Kaplan-Meier estimate of TDPPN (2 years)	2-year TDPPN (95% CI)	(0.000,)	(0.000,)
Hazard ratio (E7389/TPC)*	Estimate (95% CI)	0.790 (0.342, 1.826)	

Patients who had an existing no preexisting peripheral neuropathy (or grade 1) at baseline are considered progressed at a time such that they reach grade 2 or more for any peripheral neuropathy AE terms. Patients who had a grade 2 peripheral neuropathy at baseline are considered progressed at a time where they reach grade 3 or greater peripheral neuropathy. Patients are censored if they die or are lost to follow-up prior to development/progression. Baseline CTC has been set as grade 1 if missing.

The incidence of peripheral neuropathy appears to be related to the cumulative eribulin dose. The sponsor-conducted analysis demonstrated that the incidence of peripheral neuropathy increased from thirteen percent in subjects with a cumulative exposure of ≤ 5.6 mg/m² (2 cycles or less) to over forty percent in subjects with a cumulative exposure > 11.2 mg/m² (more than 4 cycles).

Peripheral neuropathies were reversible in many, but not all patients. In Study 305, one hundred fourteen patients (23%) developed a new or worsening neuropathy that had not recovered within a median follow-up duration of 269 days (range 20-657 days). Table 63 presents the applicant-conducted analysis of the time to resolution of treatment-emergent peripheral neuropathies. The median time to resolution of peripheral neuropathies of Grade 2 or higher severity was 8 weeks. This analysis was complicated by the lack of follow-up of adverse events after 30 days elapsed from discontinuation of study therapy. Furthermore, many patients initiated another anti-cancer therapy prior to resolution of the neuropathy. As a result, over 80% of subjects were censored. Therefore, definitive conclusions regarding the duration of peripheral neuropathies cannot be made.

Comment: Based upon review of adverse event data related to peripheral neuropathies reported in Studies 305, 201, and 211, the clinical review team recommended changes to

the proposed product labeling. A warning about peripheral neuropathies was added to the Warnings and Precautions section of the label. In addition, information regarding the incidence of motor neuropathies and dose reductions required due to neuropathies was added. Finally, information indicating that some patients enrolled in Study 305 developed neuropathies that did not resolve and specific instructions to withhold Halaven for Grade 3 or 4 neuropathies was added to the proposed label.

Table 63: Applicant-Conducted Analysis of Time to Resolution of Peripheral Neuropathy

Category	All Eribulin Treated (N=1222) n (%)	Phase II/III Breast Cancer Subjects on Target Dose (N=827) n (%)
Time to Resolution of Any Treatment-Emergent Peripheral Neuropathy with CTC Grade \geq2 (Weeks)		
Number of Subjects with Events (2)	29 (17.9)	25 (20.5)
Number of Subjects Censored (2)	133 (82.1)	97 (79.5)
25th percentile	4.71	4.71
Median	8.71	8.14
75th percentile	15.71	15.71
Min, Max (3)	0.14+, 28.14+	0.14+, 28.14+
Time to Onset of Any Treatment-Emergent Peripheral Neuropathy with CTC Grade \geq3 (Weeks)		
Number of Subjects with Events (1)	78 (6.4)	63 (7.6)
Number of Subjects Censored (1)	1144 (93.6)	764 (92.4)
25th percentile	58.14	58.14
Median	-	-
75th percentile	-	-
Min, Max (3)	0.14+, 151.14+	0.14+, 123.14+
Time to Resolution of Any Treatment-Emergent Peripheral Neuropathy with CTC Grade \geq3 to CTC Grade $<$3 (Weeks)		
Number of Subjects with Events (2)	10 (16.9)	9 (19.1)
Number of Subjects Censored (2)	49 (83.1)	38 (80.9)
25th percentile	4.71	4.71
Median	8.71	8.71
75th percentile	15.71	15.71
Min, Max (3)	0.14+, 28.14+	0.14+, 28.14+

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

(2) Percentages are based on the number of safety subjects with treatment emergent neuropathy episodes that were ongoing or resolved after the date of last dose in each integrated analysis set.

(3) += censored

Peripheral neuropathy includes neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, paraesthesia.

Neutropenia

Neutropenia is a primary safety concern with eribulin. Despite protocol-mandated dose delays and adjustments for hematologic toxicities and the use of colony-stimulating factors in 20% of eribulin-treated patients, Grade 3 and 4 neutropenia was reported in 21% and 24% of patients in the eribulin group, respectively. Eighty-one (16%) of the 503 eribulin-treated patients experienced severe-neutropenia (< 500 mcL), lasting more than one week, and febrile neutropenia occurred in 23 (5%) patients. Two patients died from complications of febrile neutropenia. Eribulin discontinuation, delay, or dose reduction due to neutropenia or febrile neutropenia occurred in 22.7% and 3.2% of eribulin-treated patients, respectively.

The applicant analyzed the time to ANC nadir and recovery using Kaplan-Meier analysis. In this analysis, patients were censored if they did not have Grade 3 or 4 ANC measurements, and the time to nadir was the earliest date of the minimum Grade 3 or 4 ANC. Of the 287 patients in the eribulin arm with recorded Grade 3 or 4 neutropenia, the median time to nadir during the entire treatment period was 78 days. The mean time to nadir within a cycle was approximately 13 days, and the median time to recovery to an ANC of 1,000 /mcL or above was 8 days.

Comment: the proposed label contains a warning regarding neutropenia and neutropenia-related complications associated with eribulin. In addition, the Dosage and Administration section contains guidelines for dose delay and reduction for neutropenia. Although severe neutropenia occurred frequently in clinical studies of eribulin, the incidence of fatal infection was low; this is probably related to the practice of appropriate dose adjustments, use of granulocyte-colony stimulating factors, effective surveillance for signs of infection, and prompt initiation of appropriate antimicrobial therapy in neutropenic patients who experience signs of potential infection. Despite the increased risk of life-threatening infection due to eribulin-induced neutropenia, the risk/benefit analysis favors treatment of this patient population with eribulin (based on the OS analysis).

Study 108 demonstrated increased eribulin exposure in patients with mild or moderate hepatic impairment. In the seven Child-Pugh A and four Child-Pugh B patients enrolled in Study 108, mean dose-normalized AUC was 1.75- and 2.79-fold that of patients with normal liver function, respectively. Consistent with the results of Study 108, the applicant-conducted integrated analysis of safety displayed a trend toward a higher incidence of serious treatment-emergent adverse events, Grade 4 neutropenia, and febrile neutropenia in patients with elevated bilirubin, AST, and ALT levels (Table 64, Table 65, and Table 66).

Table 64: Subgroup Analysis of Serious Treatment Emergent Adverse Events Based Upon Hepatic Parameters (conducted by applicant)

Hepatic Parameter	All Eribulin-Treated Patients N= 1222 n (%)	Phase II/III Breast Cancer Subjects on Target Dose N=827 n (%)
Bilirubin		
< 1 X ULN	334 of 1155 patients (29)	205 of 774 patients (27)
1-1.5 X ULN	15 of 48 patients (31)	12 of 39 patients (31)
> 1.5 X ULN	5 of 10 patients (50)	4 of 7 patients (57)
AST		
< 2.5 X ULN	319 of 1128 patients (28)	191 of 751 patients(25)
2.5-5 X ULN	30 of 78 patients (39)	26 of 64 patients (40)
> 5.0 X ULN	6 of 7 patients (85)	5 of 5 patients (100)
ALT		
< 2.5 X ULN	339 of 1178 patients (29)	208 of 790 patients (26)
2.5-5 X ULN	16 of 35 patients (46)	14 of 30 patients (47)

Table 65: Subgroup Analysis Grade 3 and 4 Neutropenia Based Upon Hepatic Parameters (conducted by applicant)

Hepatic Parameter	All Eribulin-Treated Patients N= 1222 n (%)	Phase II/III Breast Cancer Subjects on Target Dose N=827 n (%)
Bilirubin		
< 1 X ULN	519 of 1155 patients (45)	368 of 774 patients (48)
1-1.5 X ULN	26 of 48 patients (54)	22 of 39 patients (56)
> 1.5 X ULN	7 of 10 patients (70)	5 of 7 patients (72)
AST		
< 2.5 X ULN	492 of 1128 patients (44)	344 of 751 patients (46)
2.5-5 X ULN	53 of 78 patients (68)	44 of 634 patients (69)
> 5.0 X ULN	5 of 7 patients (71)	5 of 5 patients (100)
ALT		
< 2.5 X ULN	525 of 1178 patients (45)	33 of 790 patients (4)
2.5-5 X ULN	25 of 35 patients (71)	4 of 30 patients (13)
> 5 X ULN	1 of 3 patients (33)	1 of 3 patients (33)

Table 66: Subgroup Analysis of Febrile Neutropenia Based Upon Hepatic Parameters

Hepatic Parameter	All Eribulin-Treated Patients N= 1222 n (%)	Phase II/III Breast Cancer Subjects on Target Dose N=827 n (%)
Bilirubin		
< 1 X ULN	50 of 1155 patients (4)	32 of 774 patients (4)
1-1.5 X ULN	4 of 48 patients (8)	4 of 39 patients (10)
> 1.5 X ULN	2 of 10 patients (20)	5 of 7 patients (72)
AST		
< 2.5 X ULN	492 of 1128 patients (44)	344 of 751 patients (46)
2.5-5 X ULN	53 of 78 patients (68)	44 of 634 patients (69)
> 5.0 X ULN	5 of 7 patients (71)	5 of 5 patients (100)
ALT		
< 2.5 X ULN	525 of 1178 patients (45)	33 of 790 patients (4)
2.5-5 X ULN	25 of 35 patients (71)	4 of 30 patients (13)
> 5 X ULN	1 of 3 patients (33)	1 of 3 patients (33)

Comment: The label proposed by the applicant included a recommendation to (b) (4)

Based upon review of this data, FDA modified the label to include recommendation for a reduced dose of 1.1 mg/m² in patients with mild hepatic impairment (Child Pugh A) and 0.7 mg/m² in patients with moderate hepatic impairment (Child-Pugh-B). In addition, language was added in the label to advise clinicians that due to lack of safety data in patients with severe hepatic impairment, eribulin is not recommended in this population. Finally, the Warnings and Precautions section of the label was modified to include information about the higher incidence of Grade 4 neutropenia and febrile neutropenia in patients with patients with elevated AST, ALT, and bilirubin levels.

Proprietary Name Review

The Division of Medication Error Prevention and Analysis (DMEPA) submitted a review of the proposed proprietary name, Halaven, to DBOP on July 2, 2010. DMEPA had identified and evaluated a total of 32 drug names and determined that Halaven was not vulnerable to name confusion that could lead to medication errors with any currently marketed products. At the time of this review, DMEPA had no objections to the use of Halaven for the proprietary name for eribulin.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 305

In this review, common adverse events were evaluated based upon the preferred term, high level term, and high level group term of the MedDRA hierarchy for study 305. The most common adverse events (with > 10% incidence in the safety analysis population) were bone marrow suppression (neutropenia, leucopenia, anemia), alopecia, gastrointestinal (nausea, diarrhea, vomiting, constipation, nausea), constitutional (fatigue/asthenia, anorexia, weight loss, fever), pain-related (headache, back pain, bone pain, arthralgia, myalgia, extremity pain), respiratory (dyspnea, cough), and neurologic (paresthesia, and peripheral sensory neuropathy).

Comment: The proposed label uses composite terms of asthenia/fatigue, arthralgia/myalgia, and peripheral neuropathy (including the preferred terms neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, paresthesia, (b) (4)) to describe the incidences of these adverse events.

In Study 305, a total of 10,384 adverse events were reported from 727 patients. The original database included events that occurred in the interval between registration and study treatment. These events were excluded from this analysis. Of the 762 patients who were randomized and thus included in the ITT analysis, 12 patients were excluded from the safety analysis set because they did not receive study treatment (5 in the eribulin arm and 7 in the TPC arm). Therefore, the safety analysis population consists of 750 patients, 503 in the eribulin arm and 247 in the TPC arm.

Review of adverse events was complicated by the fact that 695 events in 267 patients were not assigned a CTCAE grade; instead they were coded as “mild”, “moderate”, or “severe”. For labeling purposes (but not in the datasets), the applicant converted these descriptive terms to toxicity grades based upon the following algorithm:

- Febrile neutropenia: mild or moderate, Grade 3; severe, Grade 4
- Alopecia: mild or moderate, Grade 1; severe, Grade 2
- Other: mild, Grade 1; moderate, Grade 2; severe and not serious, Grade 3; severe and serious, Grade 4.
- Any event with a Fatal outcome: Grade 5

The applicant defined an adverse event as treatment emergent if it either

- started on or after the date of administration of the first dose of study drug up until 30 days after the last dose or

- was present prior to the administration of the first dose of study drug and worsened during the study.

This resulted in 232 adverse events in the database being classified as non-treatment emergent. Eighty-eight of the 232 adverse events were classified as non-treatment emergent because they occurred prior to the first dose of treatment. A total of 26 of the 232 events occurred in patients who were randomized but did not receive therapy. The remaining 118 adverse events were considered not to be treatment emergent because they occurred more than 30 days after the last dose of treatment was administered. Sixty-nine (58%) of the total 118 adverse events occurred in patients treated with eribulin, and 49 (42%) occurred in patients treated in the TPC group.

Fifteen adverse events of Grade 3 severity or greater occurring in the eribulin group were not considered by the applicant to be treatment emergent because they occurred more than 30 days after treatment (versus 10 in the TPC arm). Of these events, 6 were considered by this reviewer to be at least possibly treatment-emergent, either because they represented worsening of an adverse event that occurred earlier in therapy, or occurred as a result of a toxicity that was related to study therapy. Five of these adverse events were fatal, but considered unrelated to study treatment by the investigator. Table 67 lists adverse events of Grade 3 or greater severity that occurred more than 30 days after cessation of eribulin treatment and were therefore flagged as non-treatment emergent by the applicant (shaded entries indicate that this reviewer considers the adverse event as at least possibly treatment emergent).

Table 67: Adverse Events of \geq Grade 3 Severity Occurring More Than 30 days After Cessation of Eribulin Therapy (Classified as Non-treatment Emergent by the Applicant)

Patient ID	Preferred Term	Serious Adverse Event?	Considered Related by Investigator?	Outcome	Time elapsed from last dose of E7389
11031004	LYMPHANGITIS	Y	NOT RELATED	FATAL	39
13011006	COMA	Y	NOT RELATED	RECOVERED/RESOLVED	73
13041001	SYNCOPE	Y	NOT RELATED	RECOVERED/RESOLVED WITH SEQUELAE	40
14011018	PARAPLEGIA	Y	NOT RELATED	FATAL	36
14021004	ASTHENIA	N	NOT RELATED	NOT RECOVERED/NOT RESOLVED	49
14021022	MALIGNANT NEOPLASM PROGRESSION	Y	NOT RELATED	FATAL	42

14091003	GENERAL PHYSICAL HEALTH DETERIORATION	Y	NOT RELATED	FATAL	34
17041001	RESPIRATORY FAILURE	Y	NOT RELATED	FATAL	31
19031011	PARAPARESIS	Y	NOT RELATED	FATAL	47
20081004	MYALGIA	N	NOT RELATED	NOT RECOVERED/NOT RESOLVED	42
23021001 ^a	DEPRESSED LEVEL OF CONSCIOUSNESS	Y	NOT RELATED	FATAL	35
24091005	DYSPNOEA	Y	NOT RELATED	FATAL	34
28111004	FRACTURE	Y	NOT RELATED	RECOVERED/RESOLVED WITH SEQUELAE	41
28191007	CLOSTRIDIUM DIFFICILE COLITIS	Y	NOT RELATED	RECOVERED/RESOLVED	34
28271002	MULTI-ORGAN FAILURE	Y	NOT RELATED	FATAL	113

^a Patient– had brain metastases

Comments regarding patients with adverse events occurring more than 30 days after therapy, but considered to be treatment emergent based upon case review:

- Patient 14011018 was hospitalized for paraplegia 11 days following the Cycle 4 Day 8 dose. Determined to be a sign of “disease progression”. Subsequent imaging revealed disease progression in “cervical” and “spinal” areas. Paraplegia was ongoing at the time of death and was considered fatal, but not treatment-related. *Comment: neurotoxicity may have been in part due to eribulin, although the event is more likely to be due to disease progression.*
- Patient 14091003 was hospitalized for general health deterioration (Grade 3) and musculoskeletal pain 14 days after receiving the Cycle 2, Day 8 dose. Treatment was discontinued. Both adverse events were ongoing at the time of death. Physical health deterioration was considered fatal and unrelated to study treatment by the investigator.
- Patient 17041001 developed respiratory failure 23 days after the Cycle 3, Day 8 dose. Imaging of the thorax revealed pleural effusion. The patient’s symptoms progressively worsened, resulting in death 8 days later. Considered unrelated to study treatment by the investigator.

- Pt 19031011 developed paraparesis leading to treatment discontinuation 16 days after the Cycle 9, Day 1 dose. This patient developed Grade 2 sensory neuropathy 3 ½ months prior to the event, which worsened to Grade 3 sensory neuropathy 9 days prior to the event. The patient also had Grade 3 pain in lower extremities and paresthesia. Paraparesis was ongoing at the time of death, and was considered fatal; it was attributed to clinical progression of breast cancer by the investigator. *Reviewer note: neurotoxicity may have been in part due to eribulin.*
- Patient 24091005 developed dyspnea 11 days after the Cycle 1, Day 8 dose of study medication. She was hospitalized and diagnosed with Grade 3 pneumonia two days later. Grade 3 pleural effusion was reported 17 days after treatment was given. Pleural effusion and pneumonia were ongoing at the time of the patient's death. Death was attributed to disease progression.
- Patient 28191007 developed pancytopenia and stomatitis 19 days after the Cycle 3, Day 8 dose of eribulin. The patient was hospitalized and treated with broad spectrum antibiotic therapy for febrile neutropenia. One day after antibiotics were discontinued, she developed loose stools, and *C. difficile* colitis (Grade 3) was diagnosed one day later (34 days after Cycle 3, Day 8 dose). Colitis resolved with oral vancomycin administration after 3 days.

Comment: In this reviewer's opinion, it is unlikely that the omission of these six adverse events substantially impacted the analysis of safety. With the exception of C. difficile colitis, the adverse events were either not likely to be related to eribulin, or occurred in the context of other contributing co-morbid conditions.

Table 68 lists treatment-emergent adverse reactions reported for Study 305 by MedDRA preferred term. The label proposed by the applicant included a table of adverse reactions that occurred at an incidence rate of at least 10% in Study 305, as well as a separate listing of adverse reactions that occurred in ≥5% but less than 10% of patients treated with eribulin. The table of adverse reactions included the composite terms "asthenia/fatigue," "arthralgia/myalgia," and "peripheral neuropathy." The composite term "peripheral neuropathy" included the following preferred terms: neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paresthesia. This reviewer recommended adding the preferred terms dysesthesia, hyperesthesia, and hypoesthesia to the composite term of peripheral neuropathy in the adverse reactions table in the proposed label.

Table 68: Adverse Reactions (per-Patient incidence rate) in Study 305 by MedDRA Preferred Term

Preferred Term (per-patient incidence)	Eribulin (N=503)				TPC (N=247)			
	All Grades		Severe ^a		All Grades		Severe ^a	
	n	%	n	%	n	%	n	%
Neutropenia	260	52	227	45	73	30	52	21
Alopecia	224	45	1	0	24	10	0	0
Nausea	174	35	6	1	70	28	7	3
Fatigue	146	29	18	4	47	19	15	6
Asthenia	136	27	33	7	58	23	14	6
Constipation	124	25	4	1	51	21	2	1
Leucopenia	116	23	70	14	28	11	14	6
Weight decreased	107	21	4	1	35	14	1	0
Pyrexia	105	21	1	0	31	13	1	0
Anorexia	98	19	3	1	32	13	3	1
Headache	97	19	2	0	29	12	1	0
Anemia	94	19	10	2	56	23	9	4
Diarrhea	92	18	0	0	45	18	0	0
Vomiting	91	18	5	1	44	18	3	1
Back pain	79	16	5	1	18	7	4	2
Dyspnoea	79	16	21	4	31	13	11	4
Cough	72	14	0	0	21	9	0	0
Arthralgia	69	14	2	0	13	5	2	1
Peripheral sensory neuropathy	62	12	9	2	10	4	2	1
Bone pain	60	12	10	2	23	9	5	2
Pain in extremity	57	11	5	1	25	10	3	1
Paresthesia	56	11	8	2	16	6	0	0
Myalgia	54	11	1	0	17	7	1	0
Urinary tract infection	49	10	4	1	13	5	0	0
Edema peripheral	46	9	2	0	21	9	3	1
Abdominal pain upper	45	9	1	0	15	6	2	1
Mucosal inflammation	43	9	7	1	25	10	5	2
Dyspepsia	42	8	1	0	8	3	0	0
Abdominal pain	39	8	5	1	20	8	2	1
Dysgeusia	39	8	0	0	5	2	0	0
Neuropathy peripheral	39	8	11	2	9	4	2	1
Dizziness	38	8	3	1	13	5	1	0
Insomnia	38	8	0	0	10	4	1	0
Stomatitis	38	8	2	0	12	5	1	0
Hypokalemia	36	7	13	3	5	2	0	0
Lacrimation increased	36	7	0	0	8	3	0	0

Preferred Term (per-patient incidence)	Eribulin (N=503)				TPC (N=247)			
	All Grades		Severe ^a		All Grades		Severe ^a	
	n	%	n	%	n	%	n	%
Muscle spasms	36	7	0	0	10	4	0	0
Musculoskeletal chest pain	36	7	1	0	15	6	1	0
Musculoskeletal pain	36	7	3	1	10	4	1	0
Pharyngolaryngeal pain	36	7	1	0	3	1	0	0
Rash	31	6	1	0	15	6	1	0
Dry mouth	28	6	0	0	3	1	0	0
Anxiety	27	5	3	1	11	4	0	0
Muscular weakness	27	5	3	1	3	1	0	0
Alanine aminotransferase increased	26	5	9	2	6	2	1	0
Upper respiratory tract infection	26	5	1	0	5	2	1	0
Depression	25	5	3	1	3	1	0	0
Nasopharyngitis	24	5	0	0	7	3	0	0
Neuropathy	24	5	7	1	6	2	0	0
Pain	24	5	2	0	15	6	3	1
Febrile neutropenia	23	5	22	4	4	2	4	2
Hypomagnesaemia	22	4	2	0	6	2	0	0
Pruritus	22	4	1	0	2	1	0	0
Rhinitis	22	4	0	0	3	1	0	0
Vertigo	22	4	2	0	5	2	0	0
Aspartate aminotransferase increased	21	4	6	1	9	4	5	2
Peripheral motor neuropathy	20	4	8	2	2	1	1	0
Weight increased	20	4	1	0	7	3	1	0
Lethargy	19	4	4	1	5	2	1	0
Hyperglycemia	18	4	6	1	6	2	2	1
Hypertension	18	4	1	0	4	2	0	0
Tachycardia	18	4	0	0	3	1	0	0
Decreased appetite	17	3	0	0	4	2	0	0
Hypoesthesia	17	3	0	0	5	2	0	0
Abdominal distension	16	3	0	0	4	2	1	0
Dysphonia	15	3	0	0	2	1	0	0
Dysuria	14	3	0	0	4	2	0	0
Hot flush	14	3	0	0	5	2	0	0
Hypercalcemia	14	3	4	1	2	1	1	0
Influenza	14	3	0	0	2	1	0	0
Gastroesophageal reflux disease	13	3	0	0	7	3	0	0

Preferred Term (per-patient incidence)	Eribulin (N=503)				TPC (N=247)			
	All Grades		Severe ^a		All Grades		Severe ^a	
	n	%	n	%	n	%	n	%
Hypotension	13	3	2	0	4	2	1	0
Lymphedema	13	3	0	0	6	2	0	0
Rhinorrhea	13	3	0	0	2	1	0	0
Somnolence	13	3	1	0	4	2	1	0
Thrombocytopenia	13	3	4	1	12	5	6	2
Chills	12	2	1	0	2	1	0	0
Conjunctivitis	12	2	0	0	8	3	0	0
Cystitis	12	2	0	0	3	1	0	0
Dehydration	12	2	3	1	6	2	4	2
Epistaxis	12	2	0	0	13	5	0	0
Hypoalbuminemia	12	2	1	0	3	1	1	0
Hypocalcaemia	12	2	2	0	2	1	0	0
Lymphopenia	12	2	6	1	7	3	1	0
Neck pain	12	2	0	0	6	2	0	0
Pharyngitis	12	2	1	0	1	0	0	0
Bronchitis	11	2	1	0	2	1	0	0
Pleural effusion	11	2	4	1	7	3	2	1
Sinusitis	11	2	0	0	2	1	0	0
Toothache	11	2	1	0	3	1	0	0
Dry skin	10	2	0	0	4	2	0	0
Flushing	10	2	0	0	4	2	0	0
Productive cough	10	2	0	0	1	0	0	0
Blood alkaline phosphatase increased	9	2	1	0	6	2	2	1
Blood lactate dehydrogenase increased	9	2	1	0	1	0	0	0
Hyperbilirubinemia	9	2	2	0	2	1	0	0
Influenza like illness	9	2	0	0	7	3	0	0
Nail disorder	9	2	0	0	7	3	0	0
Night sweats	9	2	0	0	2	1	0	0
Non-cardiac chest pain	9	2	1	0	3	1	1	0
Oral candidiasis	9	2	0	0	3	1	0	0
Polyneuropathy	9	2	2	0	2	1	0	0
Pulmonary embolism	9	2	7	1	5	2	3	1
Urinary incontinence	9	2	1	0	1	0	0	0
Cancer pain	8	2	1	0	4	2	2	1
Dysphagia	8	2	1	0	3	1	0	0
Fall	8	2	1	0	1	0	0	0
Gait disturbance	8	2	0	0	0	0	0	0

Preferred Term (per-patient incidence)	Eribulin (N=503)				TPC (N=247)			
	All Grades		Severe ^a		All Grades		Severe ^a	
	n	%	n	%	n	%	n	%
General physical health deterioration	8	2	6	1	3	1	3	1
Hypophosphatemia	8	2	3	1	1	0	1	0
Neurotoxicity	8	2	0	0	1	0	1	0
Palpitations	8	2	1	0	1	0	0	0
Ascites	7	1	0	0	9	4	2	1
Confusional state	7	1	1	0	6	2	2	1
Fecal incontinence	7	1	2	0	0	0	0	0
Gastritis	7	1	0	0	1	0	0	0
Hemorrhoids	7	1	0	0	2	1	0	0
Hypothermia	7	1	0	0	2	1	0	0
Mouth ulceration	7	1	0	0	2	1	0	0
Neutrophil count decreased	7	1	4	1	2	1	2	1
Oral herpes	7	1	0	0	0	0	0	0
Palmar-plantar erythrodysesthesia syndrome	7	1	2	0	34	14	9	4
Vision blurred	7	1	1	0	3	1	0	0
White blood cell count decreased	7	1	4	1	0	0	0	0
Blood creatinine increased	6	1	2	0	2	1	1	0
Ear pain	6	1	0	0	1	0	0	0
Erythema	6	1	0	0	9	4	0	0
Eye pain	6	1	0	0	0	0	0	0
Hyperhidrosis	6	1	0	0	1	0	0	0
Metastatic pain	6	1	3	1	1	0	0	0
Pneumonia	6	1	5	1	5	2	2	1
Pollakiuria	6	1	0	0	2	1	0	0
Tinnitus	6	1	0	0	2	1	0	0
Agitation	5	1	0	0	2	1	0	0
Balance disorder	5	1	0	0	2	1	0	0
Breath sounds abnormal	5	1	0	0	3	1	0	0
Dyspnea exertional	5	1	0	0	4	2	0	0
Flatulence	5	1	0	0	2	1	0	0
Groin pain	5	1	1	0	2	1	0	0
Hepatotoxicity	5	1	3	1	1	0	0	0
Hyperkalemia	5	1	0	0	1	0	0	0
Hypersensitivity	5	1	0	0	0	0	0	0
Laryngitis	5	1	0	0	0	0	0	0
Lower respiratory tract	5	1	0	0	3	1	1	0

Preferred Term (per-patient incidence)	Eribulin (N=503)				TPC (N=247)			
	All Grades		Severe ^a		All Grades		Severe ^a	
	n	%	n	%	n	%	n	%
infection								
Malignant neoplasm progression	5	1	4	1	3	1	2	1
Memory impairment	5	1	1	0	1	0	0	0
Migraine	5	1	0	0	0	0	0	0
Oral pain	5	1	0	0	5	2	0	0
Performance status decreased	5	1	0	0	4	2	3	1
Sciatica	5	1	1	0	2	1	0	0
Wheezing	5	1	0	0	1	0	0	0
Aphthous stomatitis	4	1	0	0	1	0	0	0
Breast pain	4	1	1	0	0	0	0	0
Candidiasis	4	1	0	0	0	0	0	0
Coordination abnormal	4	1	0	0	1	0	0	0
Depressed mood	4	1	0	0	0	0	0	0
Diplopia	4	1	0	0	0	0	0	0
Dry eye	4	1	0	0	2	1	0	0
Dysesthesia	4	1	1	0	2	1	0	0
Flank pain	4	1	0	0	0	0	0	0
Hepatomegaly	4	1	0	0	5	2	0	0
Herpes zoster	4	1	0	0	0	0	0	0
Hypoacusis	4	1	0	0	2	1	0	0
Infection	4	1	2	0	1	0	0	0
Jaundice	4	1	0	0	2	1	0	0
Liver function test abnormal	4	1	1	0	0	0	0	0
Musculoskeletal stiffness	4	1	0	0	1	0	0	0
Nasal congestion	4	1	0	0	0	0	0	0
Neutrophil count	4	1	2	0	1	0	0	0
Pain in jaw	4	1	0	0	6	2	0	0
Syncope	4	1	2	0	2	1	0	0
Thirst	4	1	0	0	0	0	0	0
Thrombosis	4	1	0	0	0	0	0	0
Tracheobronchitis	4	1	0	0	1	0	0	0
Tremor	4	1	1	0	0	0	0	0
Tumor pain	4	1	0	0	3	1	0	0
Visual acuity reduced	4	1	0	0	1	0	0	0
Axillary pain	3	1	1	0	2	1	1	0
Breast infection	3	1	0	0	0	0	0	0
Catheter related infection	3	1	2	0	0	0	0	0

Preferred Term (per-patient incidence)	Eribulin (N=503)				TPC (N=247)			
	All Grades		Severe ^a		All Grades		Severe ^a	
	n	%	n	%	n	%	n	%
Cellulitis	3	1	1	0	3	1	0	0
Contusion	3	1	0	0	3	1	0	0
Diabetes mellitus	3	1	0	0	1	0	0	0
Erysipelas	3	1	1	0	1	0	0	0
Eye irritation	3	1	0	0	2	1	0	0
Face edema	3	1	0	0	2	1	0	0
Gingival pain	3	1	0	0	2	1	0	0
Hematochezia	3	1	0	0	0	0	0	0
Hemoglobin decreased	3	1	0	0	2	1	0	0
Hepatic pain	3	1	0	0	3	1	0	0
Hypoesthesia facial	3	1	0	0	1	0	0	0
Hyponatremia	3	1	3	1	1	0	1	0
Hyporeflexia	3	1	0	0	0	0	0	0
Hypovolemia	3	1	1	0	0	0	0	0
Injection site reaction	3	1	0	0	1	0	0	0
Leukocytosis	3	1	0	0	1	0	0	0
Liver disorder	3	1	1	0	0	0	0	0
Lung infection	3	1	2	0	1	0	0	0
Malaise	3	1	0	0	1	0	1	0
Metastases to meninges	3	1	2	0	0	0	0	0
Odynophagia	3	1	0	0	0	0	0	0
Esophagitis	3	1	0	0	4	2	0	0
Oral infection	3	1	0	0	1	0	0	0
Pallor	3	1	0	0	1	0	0	0
Pelvic pain	3	1	0	0	3	1	0	0
Peripheral coldness	3	1	0	0	1	0	0	0
Photopsia	3	1	0	0	0	0	0	0
Platelet count decreased	3	1	0	0	2	1	0	0
Postnasal drip	3	1	0	0	1	0	0	0
Respiratory tract infection viral	3	1	0	0	0	0	0	0
Rhinitis allergic	3	1	0	0	1	0	0	0
Sinus headache	3	1	0	0	0	0	0	0
Tooth abscess	3	1	0	0	1	0	0	0
Tooth infection	3	1	0	0	1	0	0	0
Vaginal candidiasis	3	1	0	0	2	1	0	0

^a Includes ≥ Grade 3 adverse reactions and adverse reactions coded as “severe” in the datasets.

Table 69 presents the results from the MAED analysis of treatment-emergent adverse events by preferred term for Study 305. Shaded entries highlight the preferred terms with either low calculated p-values or high odds ratios indicating that the adverse event was more frequent in the eribulin group. All shaded entries that occurred with at least 5% incidence are described in the proposed product label.

Table 69: Adverse Reactions with a Per-patient incidence of $\geq 1\%$ in the Eribulin Treatment Arm by MedDRA Preferred Term

PT	Eribulin (N = 503)			TPC (N = 247)			Eribulin vs. TPC	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value
Neutropenia	866	260	51.69	162	73	29.55	2.55	<.0001
Alopecia	271	224	44.53	28	24	9.72	7.46	<.0001
Nausea	337	174	34.59	122	70	28.34	1.34	0.0972
Fatigue	363	146	29.03	78	47	19.03	1.74	0.0033
Asthenia	288	136	27.04	99	58	23.48	1.21	0.3293
Constipation	179	124	24.65	62	51	20.65	1.26	0.2337
Leukopenia	302	116	23.06	84	28	11.34	2.34	0.0001
Weight decreased	147	107	21.27	39	35	14.17	1.64	0.0223
Pyrexia	172	105	20.87	51	31	12.55	1.84	0.0063
Anorexia	126	98	19.48	44	32	12.96	1.63	0.0308
Headache	143	97	19.28	39	29	11.74	1.80	0.0093
Anemia	186	94	18.69	99	56	22.67	0.78	0.2076
Diarrhea	142	92	18.29	72	45	18.22	1.00	1.0000
Vomiting	141	91	18.09	69	44	17.81	1.02	1.0000
Back pain	100	79	15.71	20	18	7.29	2.37	0.0011
Dyspnoea	133	79	15.71	41	31	12.55	1.30	0.2734
Cough	98	72	14.31	27	21	8.50	1.80	0.0249
Arthralgia	98	69	13.72	16	13	5.26	2.86	0.0004
Peripheral sensory neuropathy	95	62	12.33	20	10	4.05	3.33	0.0002
Bone pain	82	60	11.93	32	23	9.31	1.32	0.3226
Pain in extremity	85	57	11.33	33	25	10.12	1.13	0.7090
Paresthesia	95	56	11.13	20	16	6.48	1.81	0.0476
Myalgia	92	54	10.74	28	17	6.88	1.63	0.1108

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PT	Eribulin (N = 503)			TPC (N = 247)			Eribulin vs. TPC	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value
Urinary tract infection	65	49	9.74	16	13	5.26	1.94	0.0473
Edema peripheral	57	46	9.15	23	21	8.50	1.08	0.8918
Abdominal pain upper	64	45	8.95	19	15	6.07	1.52	0.1985
Mucosal inflammation	58	43	8.55	35	25	10.12	0.83	0.5000
Dyspepsia	51	42	8.35	8	8	3.24	2.72	0.0077
Abdominal pain	51	39	7.75	31	20	8.10	0.95	0.8857
Dysgeusia	55	39	7.75	5	5	2.02	4.07	0.0014
Neuropathy peripheral	58	39	7.75	11	9	3.64	2.22	0.0380
Dizziness	55	38	7.55	14	13	5.26	1.47	0.2816
Insomnia	43	38	7.55	13	10	4.05	1.94	0.0800
Stomatitis	50	38	7.55	21	12	4.86	1.60	0.2123
Hypokalemia	66	36	7.16	5	5	2.02	3.73	0.0032
Lacrimation increased	50	36	7.16	9	8	3.24	2.30	0.0320
Muscle spasms	61	36	7.16	13	10	4.05	1.83	0.1066
Musculoskeletal chest pain	42	36	7.16	16	15	6.07	1.19	0.6454
Musculoskeletal pain	53	36	7.16	16	10	4.05	1.83	0.1066
Pharyngolaryngeal pain	43	36	7.16	3	3	1.21	6.27	0.0003
Rash	38	31	6.16	15	15	6.07	1.02	1.0000
Dry mouth	32	28	5.57	3	3	1.21	4.79	0.0032
Anxiety	33	27	5.37	12	11	4.45	1.22	0.7237
Muscular weakness	49	27	5.37	4	3	1.21	4.61	0.0050
Alanine aminotransferase increased	48	26	5.17	7	6	2.43	2.19	0.0866
Upper respiratory tract infection	28	26	5.17	6	5	2.02	2.64	0.0499
Depression	32	25	4.97	3	3	1.21	4.25	0.0123
Nasopharyngitis	33	24	4.77	10	7	2.83	1.72	0.2457
Neuropathy	33	24	4.77	6	6	2.43	2.01	0.1646
Pain	28	24	4.77	18	15	6.07	0.77	0.4852

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PT	Eribulin (N = 503)			TPC (N = 247)			Eribulin vs. TPC	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value
Febrile neutropenia	26	23	4.57	5	4	1.62	2.91	0.0581
Hypomagnesaemia	42	22	4.37	6	6	2.43	1.84	0.2225
Pruritus	24	22	4.37	2	2	0.81	5.60	0.0073
Rhinitis	25	22	4.37	3	3	1.21	3.72	0.0284
Vertigo	25	22	4.37	6	5	2.02	2.21	0.1431
Aspartate aminotransferase increased	47	21	4.17	14	9	3.64	1.15	0.8440
Peripheral motor neuropathy	29	20	3.98	2	2	0.81	5.07	0.0189
Weight increased	22	20	3.98	8	7	2.83	1.42	0.5339
Lethargy	24	19	3.78	6	5	2.02	1.90	0.2703
Hyperglycemia	36	18	3.58	12	6	2.43	1.49	0.5103
Hypertension	22	18	3.58	5	4	1.62	2.25	0.1694
Tachycardia	18	18	3.58	3	3	1.21	3.02	0.0964
Decreased appetite	19	17	3.38	7	4	1.62	2.13	0.2389
Hypoesthesia	20	17	3.38	7	5	2.02	1.69	0.3636
Abdominal distension	18	16	3.18	4	4	1.62	2.00	0.3340
Dysphonia	18	15	2.98	2	2	0.81	3.77	0.0693
Dysuria	14	14	2.78	4	4	1.62	1.74	0.4488
Hot flush	14	14	2.78	6	5	2.02	1.39	0.6279
Hypercalcemia	25	14	2.78	2	2	0.81	3.51	0.1059
Influenza	14	14	2.78	2	2	0.81	3.51	0.1059
Gastrooesophageal reflux disease	18	13	2.58	9	7	2.83	0.91	0.8136
Hypotension	15	13	2.58	7	4	1.62	1.61	0.6023
Lymphedema	15	13	2.58	7	6	2.43	1.07	1.0000
Rhinorrhea	25	13	2.58	3	2	0.81	3.25	0.1627
Somnolence	16	13	2.58	4	4	1.62	1.61	0.6023
Thrombocytopenia	30	13	2.58	24	12	4.86	0.52	0.1287
Chills	16	12	2.39	2	2	0.81	2.99	0.1610
Conjunctivitis	12	12	2.39	8	8	3.24	0.73	0.4796

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<i>PT</i>	<i>Eribulin (N = 503)</i>			<i>TPC (N = 247)</i>			<i>Eribulin vs. TPC</i>	
	<i>Events</i>	<i>Subjects</i>	<i>Rate (%)</i>	<i>Events</i>	<i>Subjects</i>	<i>Rate (%)</i>	<i>Odds Ratio</i>	<i>P-value</i>
Cystitis	19	12	2.39	3	3	1.21	1.99	0.4074
Dehydration	16	12	2.39	9	6	2.43	0.98	1.0000
Epistaxis	12	12	2.39	13	13	5.26	0.44	0.0504
Hypoalbuminemia	14	12	2.39	5	3	1.21	1.99	0.4074
Hypocalcaemia	18	12	2.39	2	2	0.81	2.99	0.1610
Lymphopenia	24	12	2.39	26	7	2.83	0.84	0.8054
Neck pain	15	12	2.39	7	6	2.43	0.98	1.0000
Pharyngitis	14	12	2.39	1	1	0.40	6.01	0.0708
Bronchitis	11	11	2.19	3	2	0.81	2.74	0.2392
Pleural effusion	13	11	2.19	9	7	2.83	0.77	0.6155
Sinusitis	16	11	2.19	2	2	0.81	2.74	0.2392
Toothache	14	11	2.19	4	3	1.21	1.82	0.5666
Dry skin	10	10	1.99	5	4	1.62	1.23	1.0000
Flushing	19	10	1.99	4	4	1.62	1.23	1.0000
Productive cough	11	10	1.99	2	1	0.40	4.99	0.1126
Blood alkaline phosphatase increased	12	9	1.79	8	6	2.43	0.73	0.5841
Blood lactate dehydrogenase increased	13	9	1.79	1	1	0.40	4.48	0.1784
Hyperbilirubinemia	16	9	1.79	2	2	0.81	2.23	0.5188
Influenza like illness	10	9	1.79	7	7	2.83	0.62	0.4208
Nail disorder	9	9	1.79	7	7	2.83	0.62	0.4208
Night sweats	10	9	1.79	2	2	0.81	2.23	0.5188
Non-cardiac chest pain	9	9	1.79	4	3	1.21	1.48	0.7597
Oral candidiasis	11	9	1.79	3	3	1.21	1.48	0.7597
Polyneuropathy	12	9	1.79	2	2	0.81	2.23	0.5188
Pulmonary embolism	9	9	1.79	6	5	2.02	0.88	0.7815
Urinary incontinence	10	9	1.79	1	1	0.40	4.48	0.1784
Cancer pain	9	8	1.59	5	4	1.62	0.98	1.0000

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PT	Eribulin (N = 503)			TPC (N = 247)			Eribulin vs. TPC	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value
Dysphagia	9	8	1.59	3	3	1.21	1.31	1.0000
Fall	11	8	1.59	1	1	0.40	3.98	0.2846
Gait disturbance	9	8	1.59	0	0	0.00	.	0.0581
General physical health deterioration	10	8	1.59	3	3	1.21	1.31	1.0000
Hypophosphatemia	12	8	1.59	1	1	0.40	3.98	0.2846
Neurotoxicity	11	8	1.59	1	1	0.40	3.98	0.2846
Palpitations	11	8	1.59	1	1	0.40	3.98	0.2846
Ascites	11	7	1.39	10	9	3.64	0.37	0.0587
Confusional state	7	7	1.39	7	6	2.43	0.57	0.3730
Fecal incontinence	8	7	1.39	0	0	0.00	.	0.1024
Gastritis	10	7	1.39	1	1	0.40	3.47	0.2830
Hemorrhoids	10	7	1.39	2	2	0.81	1.73	0.7253
Hypothermia	10	7	1.39	2	2	0.81	1.73	0.7253
Mouth ulceration	13	7	1.39	2	2	0.81	1.73	0.7253
Neutrophil count decreased	8	7	1.39	3	2	0.81	1.73	0.7253
Oral herpes	11	7	1.39	0	0	0.00	.	0.1024
Palmar-plantar erythrodysesthesia syndrome	7	7	1.39	83	34	13.77	0.09	<.0001
Vision blurred	7	7	1.39	3	3	1.21	1.15	1.0000
White blood cell count decreased	12	7	1.39	0	0	0.00	.	0.1024
Blood creatinine increased	9	6	1.19	3	2	0.81	1.48	1.0000
Ear pain	7	6	1.19	1	1	0.40	2.97	0.4358
Erythema	7	6	1.19	12	9	3.64	0.32	0.0472
Eye pain	8	6	1.19	0	0	0.00	.	0.1855
Hyperhidrosis	6	6	1.19	1	1	0.40	2.97	0.4358
Metastatic pain	8	6	1.19	1	1	0.40	2.97	0.4358
Pneumonia	7	6	1.19	6	5	2.02	0.58	0.3554

PT	Eribulin (N = 503)			TPC (N = 247)			Eribulin vs. TPC	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value
Pollakiuria	6	6	1.19	2	2	0.81	1.48	1.0000
Tinnitus	9	6	1.19	2	2	0.81	1.48	1.0000

Table 70 provides a comparison of \geq Grade 3 adverse events reported in eribulin-treated patients to those reported in TPC patients broken down by the specific chemotherapy regimen administered. Severe neutropenia, febrile neutropenia, hypokalemia, peripheral neuropathy, paresthesia, and neuropathy were more common in patients who received eribulin.

Table 70: Adverse Events of \geq Grade 3 Severity with a Per-Patient Incidence of at least 1% Eribulin Group by Preferred Term– Study 305

Adverse Event by PT Grade 3 and above (per patient analysis)	Eribulin % (N=503)	TPC					
		Total (%) (N=247)	Vinorel- bine % (N = 61)	Gemcita- bine % (N = 46)	Capecitabine % (N = 44)	Taxanes % (N = 38)	Anthracyclines % (N = 24)
Neutropenia	45.13	21.05	39.34	26.09	0.00	28.95	12.50
Leukopenia	13.92	5.67	8.20	10.87	0.00	7.89	0.00
Asthenia	5.17	4.86	1.64	6.52	2.27	10.53	4.17
Febrile neutropenia	4.37	1.62	1.64	2.17	0.00	0.00	4.17
Dyspnea	4.17	4.05	4.92	8.70	0.00	2.63	0.00
Fatigue	3.58	6.07	8.20	6.52	6.82	2.63	4.17
Hypokalemia	2.58	0.00	0.00	0.00	0.00	0.00	0.00
Neuropathy peripheral	2.19	0.81	1.64	0.00	0.00	0.00	0.00
Anemia	1.99	3.64	3.28	2.17	0.00	7.89	4.17
Alanine aminotransferase increased	1.79	0.40	0.00	2.17	0.00	0.00	0.00
Bone pain	1.79	1.62	1.64	0.00	2.27	2.63	0.00
Peripheral sensory neuropathy	1.79	0.81	0.00	0.00	0.00	5.26	0.00
Paresthesia	1.59	0.00	0.00	0.00	0.00	0.00	0.00
Peripheral motor neuropathy	1.59	0.40	1.64	0.00	0.00	0.00	0.00

Adverse Event by PT Grade 3 and above (per patient analysis)	Eribulin % (N=503)	TPC					
		Total (%) (N=247)	Vinorel- bine % (N = 61)	Gemcita- bine % (N = 46)	Capecitabine % (N = 44)	Taxanes % (N = 38)	Anthracyclines % (N = 24)
Mucosal inflammation	1.39	2.02	0.00	0.00	2.27	0.00	16.67
Neuropathy	1.39	0.00	0.00	0.00	0.00	0.00	0.00
Pulmonary embolism	1.39	1.21	1.64	2.17	0.00	0.00	4.17
Aspartate aminotransferase increased	1.19	2.02	1.64	6.52	0.00	2.63	0.00
Hyperglycemia	1.19	0.81	3.28	0.00	0.00	0.00	0.00
Lymphopenia	1.19	0.40	0.00	0.00	0.00	2.63	0.00
Nausea	1.19	2.43	3.28	0.00	4.55	0.00	8.33

Adverse Events were not coded by MedDRA high level term in the database provided by the Applicant. Table 71 lists adverse events by MedDRA high level term, as compiled by the MAED database tool. This reviewer analyzed all HLT events with a $\geq 10\%$ incidence and any additional adverse events with odds ratios above 3 or p-values < 0.05 (highlighted in bold in Table 71). Details of the HLT analyses are described below.

Analysis of HLTs with a per-patient incidence rate of $\geq 10\%$:

- Asthenic conditions: The incidence of this HLT (54%) is identical to that of the composite term asthenia/fatigue described in the label.
- Neutropenias: This incidence of this HLT (54%) is close to that described for the preferred term of neutropenia (52%) described in the label.
- Alopecias: The incidence of this HLT (45%) is identical to that described for the preferred term of alopecia in the label.
- Nausea and vomiting symptoms: The incidence of this HLT (38%) is similar to that described for the preferred term nausea (35%) in the label. In addition, the label describes the incidence of the preferred term vomiting (18%).
- Musculoskeletal signs and symptoms: The HLT “musculoskeletal signs and symptoms” refers to various signs of musculoskeletal pain and stiffness and is non-descriptive. The most common preferred terms in this category, back pain and bone pain, arthralgia, myalgia, and pain in extremity, are included in the label.
- The incidence of HLT “gastrointestinal atonic and hypomotility disorders” (26%) and the incidence of the PT “constipation” (25%) are similar.

- Physical examination procedures: This HLT includes the preferred term weight decreased (21%), weight increased (4%), and breath sounds abnormal (1%). The PT “weight decreased” is included in the adverse reactions section of the product label. Addition of “the composite HLT term in the label is not recommended because the HLT encompasses PTs that do not relate to each other (i.e., not a unified concept).
- Leukopenias: This HLT primarily reflects the preferred term “Leukopenia” (23%). Because low white blood cell counts caused by eribulin are primarily due to neutropenia, which is already described in the proposed label, including the preferred term “leucopenia” would not add substantive information. The other preferred term included in this HLT, lymphopenia, had a low incidence rate (2%).
- Peripheral Neuropathies NEC: This HLT has a lower incidence (24%) than the composite term “peripheral neuropathy” (36%) because the HLT does not include the preferred terms neuropathy, paresthesia, dysesthesia, hyperesthesia, and hypoesthesia. *In this reviewer’s opinion, the composite term used in the label is more informative than the HLT term.*
- Appetite Disorders: The incidence of this HLT (22%) is similar to the incidence of the preferred term “anorexia” (20%), which is included in the proposed label.
- Febrile Disorders: The incidence of this HLT (21%) is similar to the incidence of the preferred term “pyrexia” (21%), which is included in the proposed label.
- Headaches: The incidence of this HLT (19%) is identical to the incidence of the preferred term “headaches”, which is included in the proposed label.
- Upper respiratory tract infections: This HLT primarily reflects the preferred terms “upper respiratory tract infection” (5% incidence) and “nasopharyngitis” (5% incidence), which are included in the product label. The other preferred terms included in this HLT, “rhinitis”, “pharyngitis”, “sinusitis” “laryngitis”, and “tracheobronchitis” occurred in less than 5% of patients and were generally of Grade 2 or lesser severity; therefore, the addition of these preferred terms does not substantively add to the adverse reactions described in the label.
- Anemias NEC: The incidence of this HLT is identical to the incidence of the preferred term “anemia” (19%), which is included in the proposed product label.
- Diarrhea (excl infective): The incidence of the HLT is identical to the incidence of the preferred term “diarrhea” (18%), which is included in the proposed label.
- Breathing abnormalities: The incidence of this HLT is identical to the incidence of the preferred term “dyspnea” which is included in the proposed label.
- Coughing and associated symptoms: The incidence of this HLT (16%) is similar to the incidence of the preferred term “cough” (14%), which is included in the proposed label.
- Gastrointestinal and abdominal pains: this HLT primarily reflects the incidence of the preferred terms “abdominal pain upper” (9%), and “abdominal pain” (8%), which are described in the proposed label.

- Joint related signs and symptoms: This incidence of this HLT (15%) is similar to the incidence of the preferred term “arthralgia” (14%). This preferred term is included in the composite term “arthralgia/myalgia” that is described in the proposed label.
- The preferred terms included in the HLT “Paresthesias and dysesthesias” are reflected in the composite term “peripheral neuropathy” that is included in the product label.
- Upper respiratory tract signs and symptoms: The most common preferred terms reflected in this HLT are “dysphonia”, “rhinorrhea”, “and post-nasal drip”. The incidence of these preferred terms were less than 5% each, and all the adverse events for these preferred terms were of Grade 1 or 2 severity. *This reviewer does not believe that their inclusion would provide substantive new information, because these are signs and symptoms of upper respiratory tract infections; the preferred terms “upper respiratory tract infection” and “nasopharyngitis” are included in the proposed label.*
- Bone related signs and symptoms: The incidence of this HLT is identical to the incidence of the preferred term “bone pain”, which is included in the proposed label.
- Urinary tract infections: the incidence of this HLT is similar to the incidence of the preferred term “urinary tract infection”, which is included in the proposed label.
- Muscle pains: the incidence of this HLT is identical to the incidence of the preferred term “myalgia.” “Myalgia” is included in the composite term “arthralgia/myalgia,” which is described in the proposed label.

The following additional HLTs with odds ratios above 3 or p-values < 0.05 were also reviewed:

- Sensory abnormalities: The preferred terms that comprise this HLT were limited to dysgeusia (8%) and hypoesthesia (3%). These preferred terms are included in the proposed label. Additionally, these terms refer to disparate concepts better described by the respective PTs.
- Dyspeptic signs and symptoms: The incidence of this HLT is identical to the incidence of the preferred term “dyspepsia”, which is included in the proposed label.
- Lacrimal disorders: The incidence of this HLT (8%) is similar to that of the preferred term “increased lacrimation” (7%), which is included in the proposed label.
- Potassium balance: The incidence of this HLT is identical to the incidence of the preferred term “hypokalemia,”, which is included in the proposed label.
- Oral dryness and saliva altered: the preferred term “dry mouth” is included in the proposed label.
- Muscle weakness conditions: the preferred term “muscle weakness” is included in the proposed label.
- Calcium metabolism disorders: The preferred terms that comprise this HLT were limited to hypocalcemia (2%) and hypercalcemia (3%). As discussed in Section

7.4.2 of this review, there is insufficient evidence of eribulin causality to include these adverse events in the product label.

- Depressive disorders: the preferred term “depression” is included in the proposed label. *See analysis of depression included in section 7.3.4 for more details.*
- Pruritis NEC: The most common preferred term in this HLT was “pruritus”, which had an incidence of 4.4%. All but one of the pruritis adverse events were grade 1 or 2, and none of the adverse events resulted in discontinuation of eribulin. *The preferred term “rash” is included in the proposed label. This reviewer concludes that inclusion of the preferred term “pruritus” would not add useful information to the product label.*

Table 71: Adverse Events with Per Patient Incidence \geq 3% by MedDRA High Level Term

HLT	Eribulin (N = 503)			TPC (N = 247)			Eribulin vs. TPC	
	Events	n	Rate (%)	Events	n	Rate (%)	OR	P-value
Asthenic conditions	656	270	53.68	180	98	39.68	1.76	0.0003
Neutropenias	892	270	53.68	167	74	29.96	2.71	<.0001
Alopecias	271	224	44.53	28	24	9.72	7.46	<.0001
Nausea and vomiting symptoms	478	193	38.37	191	81	32.79	1.28	0.1467
Musculoskeletal and connective tissue signs and symptoms NEC	310	172	34.19	95	55	22.27	1.81	0.0009
Gastrointestinal atonic and hypomotility disorders NEC	197	131	26.04	71	55	22.27	1.23	0.2810
Physical examination procedures	183	130	25.84	55	45	18.22	1.56	0.0216
Leukopenias NEC	327	120	23.86	111	29	11.74	2.36	<.0001
Peripheral neuropathies NEC	216	120	23.86	39	24	9.72	2.91	<.0001
Appetite disorders	145	113	22.47	52	36	14.57	1.70	0.0113
Febrile disorders	172	105	20.87	51	31	12.55	1.84	0.0063
Headaches NEC	147	98	19.48	39	29	11.74	1.82	0.0094
Upper respiratory tract infections	128	96	19.09	26	20	8.10	2.68	<.0001
Anemias NEC	186	94	18.69	99	56	22.67	0.78	0.2076

<i>HLT</i>	<i>Eribulin (N = 503)</i>			<i>TPC (N = 247)</i>			<i>Eribulin vs. TPC</i>	
	<i>Events</i>	<i>n</i>	<i>Rate (%)</i>	<i>Events</i>	<i>n</i>	<i>Rate (%)</i>	<i>OR</i>	<i>P-value</i>
Diarrhea (excl infective)	142	92	18.29	72	45	18.22	1.00	1.0000
Breathing abnormalities	141	84	16.70	46	35	14.17	1.21	0.3966
Coughing and associated symptoms	112	80	15.90	33	24	9.72	1.76	0.0242
Gastrointestinal and abdominal pains (excl oral and throat)	121	79	15.71	58	37	14.98	1.06	0.8306
Joint related signs and symptoms	104	74	14.71	18	15	6.07	2.67	0.0004
Paresthesias and dysesthesias	126	73	14.51	29	22	8.91	1.74	0.0351
Upper respiratory tract signs and symptoms	94	63	12.52	11	9	3.64	3.79	<.0001
Bone related signs and symptoms	87	62	12.33	39	29	11.74	1.06	0.9054
Urinary tract infections	86	60	11.93	19	16	6.48	1.96	0.0204
Muscle pains	92	54	10.74	28	17	6.88	1.63	0.1108
Edema NEC	61	49	9.74	27	24	9.72	1.00	1.0000
Stomatitis and ulceration	68	49	9.74	25	15	6.07	1.67	0.0967
Sensory abnormalities NEC	63	46	9.15	10	9	3.64	2.66	0.0068
Dyspeptic signs and symptoms	53	44	8.75	8	8	3.24	2.86	0.0054
Mucosal findings abnormal	61	44	8.75	36	26	10.53	0.81	0.4262
Lacrimal disorders	55	40	7.95	12	10	4.05	2.05	0.0440
Neurological signs and symptoms NEC	55	38	7.55	14	13	5.26	1.47	0.2816
Potassium imbalance	74	38	7.55	9	6	2.43	3.28	0.0045
Muscle related signs and symptoms NEC	63	37	7.36	13	10	4.05	1.88	0.1077

<i>HLT</i>	<i>Eribulin (N = 503)</i>			<i>TPC (N = 247)</i>			<i>Eribulin vs. TPC</i>	
	<i>Events</i>	<i>n</i>	<i>Rate (%)</i>	<i>Events</i>	<i>n</i>	<i>Rate (%)</i>	<i>OR</i>	<i>P-value</i>
Disturbances in consciousness NEC	44	36	7.16	12	11	4.45	1.65	0.1990
Liver function analyses	104	36	7.16	32	16	6.48	1.11	0.8786
Pain and discomfort NEC	40	35	6.96	24	20	8.10	0.85	0.5553
Anxiety symptoms	38	32	6.36	14	13	5.26	1.22	0.6257
Rashes, eruptions and exanthems NEC	39	32	6.36	15	15	6.07	1.05	1.0000
Bladder and urethral symptoms	33	29	5.77	7	7	2.83	2.10	0.1008
General signs and symptoms NEC	35	29	5.77	22	19	7.69	0.73	0.3416
Oral dryness and saliva altered	32	28	5.57	3	3	1.21	4.79	0.0032
Inner ear signs and symptoms	34	27	5.37	8	6	2.43	2.28	0.0867
Muscle weakness conditions	49	27	5.37	4	3	1.21	4.61	0.0050
Calcium metabolism disorders	43	26	5.17	4	4	1.62	3.31	0.0177
Lower respiratory tract and lung infections	30	26	5.17	16	13	5.26	0.98	1.0000
Depressive disorders	32	25	4.97	3	3	1.21	4.25	0.0123
Peripheral vascular disorders NEC	33	24	4.77	10	9	3.64	1.32	0.5721
Pruritus NEC	26	24	4.77	2	2	0.81	6.14	0.0047
Magnesium metabolism disorders	43	23	4.57	6	6	2.43	1.92	0.2254
Dermal and epidermal conditions NEC	24	21	4.17	13	11	4.45	0.93	0.8494
Flatulence, bloating and distension	23	21	4.17	6	6	2.43	1.75	0.2981
Oncologic complications and emergencies	27	21	4.17	13	9	3.64	1.15	0.8440
Rate and rhythm disorders NEC	19	19	3.78	4	4	1.62	2.38	0.1198

HLT	Eribulin (N = 503)			TPC (N = 247)			Eribulin vs. TPC	
	Events	n	Rate (%)	Events	n	Rate (%)	OR	P-value
Vascular hypertensive disorders NEC	22	18	3.58	5	4	1.62	2.25	0.1694
Body temperature perception	21	17	3.38	4	4	1.62	2.13	0.2389
Gastrointestinal signs and symptoms NEC	20	17	3.38	5	5	2.02	1.69	0.3636
White blood cell analyses	26	16	3.18	5	3	1.21	2.67	0.1390

Table 72 presents a comparison of the incidence of adverse events by HLT in the eribulin group with the major chemotherapies administered in the TPC group.

Table 72: Adverse Events with Per Patient Incidence \geq 3% in the Eribulin Group by MedDRA High Level Term – Comparison with TPC Subgroups

Adverse Event by HLT (per patient analysis)	Eribulin % (N = 503)	TPC					
		Total % (N = 247)	Vinorelbine % (N = 61)	Gemcitabine % (N = 46)	Capecitabine % (N = 44)	Taxanes % (N = 38)	Anthracyclines % (N = 24)
Asthenic conditions	53.68	39.68	50.82	36.96	38.64	44.74	33.33
Neutropenias	53.68	29.96	49.18	36.96	4.55	39.47	20.83
Alopecias	44.53	9.72	3.28	6.52	6.82	34.21	4.17
Nausea and vomiting symptoms	38.37	32.79	39.34	39.13	27.27	31.58	29.17
Musculoskeletal and connective tissue signs and symptoms NEC	34.19	22.27	32.79	15.22	29.55	26.32	4.17
Gastrointestinal atonic and hypomotility disorders NEC	26.04	22.27	40.98	19.57	15.91	21.05	8.33
Physical examination procedures	25.84	18.22	16.39	13.04	20.45	31.58	12.50
Leukopenias NEC	23.86	11.74	16.39	17.39	2.27	18.42	4.17
Peripheral neuropathies NEC	23.86	9.72	9.84	0.00	6.82	34.21	0.00
Appetite disorders	22.47	14.57	19.67	17.39	15.91	15.79	12.50

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Adverse Event by HLT (per patient analysis)	Eribulin	TPC					
	% (N = 503)	Total % (N = 247)	Vinorelbine % (N = 61)	Gemcitabine % (N = 46)	Capecitabine % (N = 44)	Taxanes % (N = 38)	Anthracyclines % (N = 24)
Febrile disorders	20.87	12.55	9.84	17.39	13.64	21.05	4.17
Headaches NEC	19.48	11.74	14.75	13.04	18.18	10.53	8.33
Upper respiratory tract infections	19.09	8.10	8.20	8.70	9.09	7.89	12.50
Anemias NEC	18.69	22.67	21.31	19.57	22.73	36.84	16.67
Diarrhea (excl infective)	18.29	18.22	22.95	19.57	27.27	13.16	4.17
Breathing abnormalities	16.70	14.17	14.75	13.04	6.82	23.68	12.50
Coughing and associated symptoms	15.90	9.72	6.56	15.22	9.09	10.53	12.50
Gastrointestinal and abdominal pains (excl oral and throat)	15.71	14.98	19.67	23.91	13.64	13.16	4.17
Joint related signs and symptoms	14.71	6.07	3.28	4.35	11.36	13.16	0.00
Paresthesias and dysesthesias	14.51	8.91	13.11	6.52	6.82	15.79	4.17
Upper respiratory tract signs and symptoms	12.52	3.64	1.64	2.17	6.82	7.89	4.17
Bone related signs and symptoms	12.33	11.74	13.11	8.70	9.09	15.79	12.50
Urinary tract infections	11.93	6.48	9.84	6.52	2.27	7.89	8.33
Muscle pains	10.74	6.88	8.20	2.17	9.09	15.79	4.17
Edema NEC	9.74	9.72	4.92	10.87	11.36	18.42	8.33
Stomatitis and ulceration	9.74	6.07	4.92	0.00	11.36	5.26	20.83
Sensory abnormalities NEC	9.15	3.64	4.92	0.00	6.82	7.89	0.00
Dyspeptic signs and symptoms	8.75	3.24	6.56	2.17	0.00	5.26	4.17
Mucosal findings abnormal	8.75	10.53	4.92	6.52	15.91	15.79	29.17
Lacrimal disorders	7.95	4.05	0.00	2.17	4.55	10.53	8.33
Neurological signs and symptoms NEC	7.55	5.26	6.56	4.35	4.55	7.89	8.33
Potassium imbalance	7.55	2.43	0.00	0.00	2.27	10.53	0.00

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Adverse Event by HLT (per patient analysis)	Eribulin % (N = 503)	TPC					
		Total % (N = 247)	Vinorelbine % (N = 61)	Gemcitabine % (N = 46)	Capecitabine % (N = 44)	Taxanes % (N = 38)	Anthracyclines % (N = 24)
Muscle related signs and symptoms NEC	7.36	4.05	11.48	0.00	2.27	2.63	0.00
Disturbances in consciousness NEC	7.16	4.45	8.20	4.35	2.27	0.00	4.17
Liver function analyses	7.16	6.48	8.20	13.04	0.00	7.89	0.00
Pain and discomfort NEC	6.96	8.10	11.48	6.52	4.55	10.53	0.00
Anxiety symptoms	6.36	5.26	4.92	8.70	2.27	5.26	8.33
Rashes, eruptions and exanthems NEC	6.36	6.07	4.92	4.35	6.82	7.89	16.67
Bladder and urethral symptoms	5.77	2.83	3.28	2.17	4.55	2.63	4.17
General signs and symptoms NEC	5.77	7.69	9.84	10.87	9.09	5.26	0.00
Oral dryness and saliva altered	5.57	1.21	3.28	0.00	0.00	0.00	0.00
Inner ear signs and symptoms	5.37	2.43	0.00	2.17	2.27	5.26	4.17
Muscle weakness conditions	5.37	1.21	1.64	2.17	0.00	0.00	4.17
Calcium metabolism disorders	5.17	1.62	1.64	2.17	0.00	0.00	4.17
Lower respiratory tract and lung infections	5.17	5.26	3.28	6.52	6.82	7.89	4.17
Depressive disorders	4.97	1.21	3.28	0.00	0.00	2.63	0.00
Peripheral vascular disorders NEC	4.77	3.64	4.92	0.00	4.55	10.53	0.00
Pruritus NEC	4.77	0.81	3.28	0.00	0.00	0.00	0.00
Magnesium metabolism disorders	4.57	2.43	3.28	0.00	4.55	5.26	0.00
Dermal and epidermal conditions NEC	4.17	4.45	0.00	0.00	6.82	10.53	12.50
Flatulence, bloating and distension	4.17	2.43	1.64	8.70	0.00	0.00	4.17
Oncologic complications and emergencies	4.17	3.64	4.92	4.35	2.27	2.63	0.00

Adverse Event by HLT (per patient analysis)	Eribulin % (N = 503)	TPC					
		Total % (N = 247)	Vinorelbine % (N = 61)	Gemcitabine % (N = 46)	Capecitabine % (N = 44)	Taxanes % (N = 38)	Anthracyclines % (N = 24)
Rate and rhythm disorders NEC	3.78	1.62	0.00	2.17	2.27	2.63	0.00
Vascular hypertensive disorders NEC	3.58	1.62	0.00	2.17	2.27	2.63	0.00
Body temperature perception	3.38	1.62	1.64	2.17	2.27	2.63	0.00
Gastrointestinal signs and symptoms NEC	3.38	2.02	1.64	2.17	2.27	2.63	4.17
White blood cell analyses	3.18	1.21	1.64	0.00	0.00	2.63	0.00

The following table shows the results of the High Level Group Term (HLGT) analysis of treatment emergent adverse events for Study 305. In general, the HLGTs evaluated in this review were non-granular terms and comprised concepts that were too disparate to add substantive information to the adverse reactions described in proposed product labeling. Nevertheless, the following HLGTs were analyzed because they appeared with high frequency and were not clearly related to a specific HLT that was already discussed:

- General system disorders: This HLGT includes unrelated preferred terms including fatigue, disease progression, and pain. Thus, this HLGT term is not appropriate for inclusion in the product label.
- White blood cell disorders: The primary adverse event within the HLGT “white blood cell disorders” in study 305 was neutropenia, which is a better descriptive term than white blood cell disorders.
- Skin appendage conditions: The primary preferred term within this HLGT, “alopecia”, is a more specific term that is included in the proposed label.
- Infections – pathogen unspecified: This HLGT includes a diverse array of infections that have different clinical implications. The most commonly reported PT in this HLGT was urinary tract infection (10%, described in the proposed label), followed by upper respiratory tract infection (5%), nasopharyngitis (5%), rhinitis (4%), influenza (3%), cystitis (2%), and pharyngitis (2%).

Table 73: Adverse Events in Study 305 by MedDRA High Level Group Term (HLGT)

HLGT	Eribulin (N = 503)			TPC (N = 247)			Eribulin vs. TPC	
	Events	n	Rate (%)	Events	n	Rate (%)	OR	P-value
General system disorders NEC	862	315	62.62	289	136	55.06	1.37	0.0478
White blood cell disorders	1228	287	57.06	280	81	32.79	2.72	<.0001
Gastrointestinal signs and symptoms	696	246	48.91	268	100	40.49	1.41	0.0353
Skin appendage conditions	300	233	46.32	42	32	12.96	5.80	<.0001
Gastrointestinal motility and defecation conditions	339	176	34.99	143	87	35.22	0.99	1.0000
Infections - pathogen unspecified	301	174	34.59	76	53	21.46	1.94	0.0002
Musculoskeletal and connective tissue disorders NEC	318	172	34.19	97	55	22.27	1.81	0.0009
Neurological disorders NEC	320	172	34.19	70	51	20.65	2.00	0.0001
Respiratory disorders NEC	359	171	34.00	93	55	22.27	1.80	0.0010
Peripheral neuropathies	230	130	25.84	41	26	10.53	2.96	<.0001
Physical examination topics	183	130	25.84	55	45	18.22	1.56	0.0216
Body temperature conditions	204	119	23.66	57	36	14.57	1.82	0.0039
Appetite and general nutritional disorders	145	113	22.47	52	36	14.57	1.70	0.0113
Muscle disorders	205	108	21.47	45	28	11.34	2.14	0.0006
Headaches	156	101	20.08	39	29	11.74	1.89	0.0041
Anemias nonhemolytic and marrow depression	189	95	18.89	99	56	22.67	0.79	0.2451
Epidermal and dermal conditions	112	80	15.90	50	36	14.57	1.11	0.6687

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<i>HLGT</i>	<i>Eribulin (N = 503)</i>			<i>TPC (N = 247)</i>			<i>Eribulin vs. TPC</i>	
	<i>Events</i>	<i>n</i>	<i>Rate (%)</i>	<i>Events</i>	<i>n</i>	<i>Rate (%)</i>	<i>OR</i>	<i>P-value</i>
Joint disorders	105	75	14.91	18	15	6.07	2.71	0.0003
Bone disorders (excl congenital and fractures)	89	64	12.72	39	29	11.74	1.10	0.7255
Oral soft tissue conditions	87	62	12.33	34	24	9.72	1.31	0.3302
Electrolyte and fluid balance conditions	106	53	10.54	22	15	6.07	1.82	0.0574
Bone, calcium, magnesium and phosphorus metabolism disorders	99	51	10.14	11	10	4.05	2.67	0.0041
Eye disorders NEC	66	44	8.75	12	10	4.05	2.27	0.0233
Sleep disorders and disturbances	44	39	7.75	13	10	4.05	1.99	0.0593
Hepatobiliary investigations	104	36	7.16	32	16	6.48	1.11	0.8786
Anxiety disorders and symptoms	39	33	6.56	14	13	5.26	1.26	0.5223
Urinary tract signs and symptoms	39	32	6.36	16	13	5.26	1.22	0.6257
Viral infectious disorders	39	32	6.36	5	4	1.62	4.13	0.0033
Hepatic and hepatobiliary disorders	40	30	5.96	16	13	5.26	1.14	0.7417
Depressed mood disorders and disturbances	37	29	5.77	3	3	1.21	4.98	0.0032
Salivary gland conditions	32	28	5.57	3	3	1.21	4.79	0.0032
Inner ear and VIIIth cranial nerve disorders	34	27	5.37	8	6	2.43	2.28	0.0867
Vascular disorders NEC	36	27	5.37	11	10	4.05	1.34	0.4786
Upper respiratory tract disorders (excl infections)	28	26	5.17	19	16	6.48	0.79	0.5002

<i>HLGT</i>	<i>Eribulin (N = 503)</i>			<i>TPC (N = 247)</i>			<i>Eribulin vs. TPC</i>	
	<i>Events</i>	<i>n</i>	<i>Rate (%)</i>	<i>Events</i>	<i>n</i>	<i>Rate (%)</i>	<i>OR</i>	<i>P-value</i>
Hematology investigations (incl blood groups)	40	24	4.77	13	7	2.83	1.72	0.2457
Cardiac arrhythmias	23	22	4.37	6	6	2.43	1.84	0.2225
Cancer-related morbidities	27	21	4.17	13	9	3.64	1.15	0.8440
Fungal infectious disorders	24	21	4.17	8	7	2.83	1.49	0.4185
Vision disorders	22	19	3.78	5	5	2.02	1.90	0.2703
Vascular hypertensive disorders	22	18	3.58	5	4	1.62	2.25	0.1694
Dental and gingival conditions	22	17	3.38	12	7	2.83	1.20	0.8267
Ocular infections, irritations and inflammations	18	17	3.38	10	10	4.05	0.83	0.6785
Decreased and nonspecific blood pressure disorders and shock	18	16	3.18	9	6	2.43	1.32	0.6513

Table 74 shows the incidence of adverse reactions by MedDRA preferred term for all eribulin-treated patients that were included in the integrated summary of safety (N=1222). In general, the incidence of adverse events reported for all eribulin-treated patients was comparable to slightly higher than that reported for eribulin-treated patients in Study 305. The following adverse events occurred with an incidence that was at least 5% higher in all eribulin-treated patients group (N=1,222) compared to the eribulin-treated group in Study 305 (N=503) [only those adverse events occurring with at least a 5% incidence are included]:

- Asthenia/fatigue was reported in 60% of all eribulin-treated patients compared to 54% of eribulin-treated patients in Study 305; however, the incidences of Grade 3 and higher asthenia/fatigue were comparable.
- Neuropathy peripheral was reported in 15% of all eribulin-treated patients included in the ISS, compared to 8% of patients in the eribulin group in Study 305; however, the incidences of the composite term “peripheral neuropathy” (which includes the preferred terms neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, and paresthesia) were comparable.

- Decreased appetite was reported in 27% of all eribulin-treated patients, compared to 20% of patients in Study 305; however, the incidences of Grade 3 or higher severity for this preferred term were the same in the two groups.
- Anemia was reported in 26% of all eribulin-treated patients in the ISS, compared to 19% of eribulin-treated patients in Study 305; however, incidences of Grade 3 or higher severity for this preferred term were the same in the two groups.

This reviewer concludes that the overall profile of adverse events reported in all-eribulin treated patients (N=1,222) included in the integrated summary of efficacy is similar to that reported in the eribulin group for Study 305 (n=305). Based upon this review, no additional changes to the label are recommended.

Table 74: Per-Patient Incidence of Treatment Emergent Adverse Events by Preferred Term (All Eribulin-Treated Patients)

Preferred Term N=1222	All Grades	All Grades (%)	Grades 3-5	Grade 3-5 (%)
Asthenia + Fatigue (1)	736	60	132	11
Neutropenia	651	53	564	46
Alopecia	535	44	0	0
Peripheral Neuropathy Based On Broad MedDRA SMQ(1)	497	41	93	8
Nausea	479	39	21	2
Fatigue	476	39	70	6
Peripheral Neuropathy (1)	404	33	79	6
Constipation	354	29	12	1
Decreased Appetite	332	27	9	1
Anemia	316	26	30	2
Asthenia	305	25	66	5
Pyrexia	285	23	13	1
Arthralgia + Myalgia (1)	263	22	16	1
Leukopenia	258	21	157	13
Diarrhea	253	21	13	1
Vomiting	251	21	19	2
Dyspnea	229	19	70	6
Headache	212	17	10	1
Cough	209	17	7	1
Neuropathy Peripheral	182	15	32	3
Weight Decreased	177	14	8	1
Back Pain	171	14	20	2
Arthralgia	165	14	14	1
Edema Peripheral	164	13	8	1
Myalgia	132	11	3	0
Pain In Extremity	129	11	12	1
Urinary Tract Infection	127	10	6	0
Bone Pain	125	10	26	2
Peripheral Sensory Neuropathy	119	10	17	1
Dizziness	118	10	3	0
Paresthesia	118	10	18	1
Abdominal Pain	115	9	19	2
Stomatitis	114	9	10	1
Mucosal Inflammation	113	9	14	1
Insomnia	113	9	1	0
Dysgeusia	103	8	0	0
Musculoskeletal Pain	101	8	11	1

Preferred Term N=1222	All Grades	All Grades (%)	Grades 3-5	Grade 3-5 (%)
Hypokalemia	99	8	27	2
Dyspepsia	96	8	3	0
Pain	86	7	17	1
Abdominal Pain Upper	85	7	5	0
Anxiety	81	7	8	1
Dry Mouth	80	7	0	0
Oropharyngeal Pain	80	7	1	0
Musculoskeletal Chest Pain	78	6	6	0
Lacrimation Increased	76	6	0	0
Muscle Spasms	75	6	2	0
Rash	75	6	3	0
Muscular Weakness	71	6	9	1
Depression	71	6	6	0
Upper Respiratory Tract Infection	70	6	1	0
Febrile Neutropenia	57	5	57	5
Dehydration	57	5	18	1
Hypomagnesaemia	56	5	3	0
Pruritus	51	4	1	0
Abdominal Distension	50	4	2	0
Tachycardia	49	4	1	0
Thrombocytopenia	48	4	14	1
Chest Pain	48	4	5	0
Alanine Aminotransferase Increased	47	4	11	1
Aspartate Aminotransferase Increased	47	4	13	1
Nasopharyngitis	46	4	0	0
Hyperglycemia	45	4	18	1
Chills	43	4	3	0
Hypoesthesia	42	3	1	0
Dysphonia	42	3	0	0
Epistaxis	40	3	1	0
Pleural Effusion	40	3	16	1
Vertigo	38	3	3	0
Hot Flush	38	3	0	0
Hypotension	38	3	7	1
Gastroesophageal Reflux Disease	36	3	0	0
Peripheral Motor Neuropathy	36	3	13	1
Night Sweats	34	3	0	0
Rhinitis	32	3	0	0
Sinusitis	32	3	1	0

Preferred Term N=1222	All Grades	All Grades (%)	Grades 3-5	Grade 3-5 (%)
Dysuria	32	3	0	0
Dyspnoea Exertional	32	3	1	0
Rhinorrhea	32	3	0	0
Neck Pain	31	3	0	0

7.4.2 Laboratory Findings

Biochemistry

The Schedule of Assessments included in the Protocol for Study 305 indicated that serum biochemistry parameters (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, total protein, and sodium) were to be performed at screening. With the exception of serum glucose, which was recorded only at baseline, the same biochemistry parameters were assessed on Days 1 and 8 of each cycle, on Day 15 of Cycles 1 and 2, at the Study Termination Visit, and when clinically indicated for patients randomized to the receive eribulin. The protocol for Study 305 stated that patients randomized to receive TPC were to be followed according to standard practice for the chosen treatment, with the exception of tumor assessments, screening assessments, study termination assessments, and collection of adverse event and concomitant medication data, which were mandated to be identical to that of patients randomized to receive eribulin. *The lack of uniform assessment of laboratory data during study 305 makes comparison of data between treatment arms difficult; laboratory abnormalities may have been underreported in the TPC arm because the patients in this arm may not have undergone the same number and types of laboratory tests during the course of their treatment).*

The laboratory datasets included Système International (SI) units in addition to conventional units used in the United States. Toxicity grades were assigned to each laboratory measurement based upon NCI CTCAE version 3.0 criteria. For the purposes of this discussion, laboratory data is expressed using SI units.

Sodium

The lower limit of normal in the laboratory datasets submitted was 135 mmol/L and the upper limit of normal was 145 mmol/L. In study 305, 17 (3%) eribulin-treated subjects experienced sodium abnormalities (<130 mmol/L or > 155 mmol/L) with a maximum toxicity Grade of 3 and 20 (4%) subjects experienced sodium abnormalities with a maximum toxicity Grade of 4 (<120 mmol/L or > 160 mmol/L). This was comparable to the TPC group, in which 10 (4%) and 7 (3%) patients experienced sodium

abnormalities up to a maximum toxicity Grade of 3 and 4, respectively. Among patients with Grade 0 or 1 baseline sodium levels, maximum Grade 3 or 4 sodium abnormalities were reported in 6.5% of patients in the eribulin group, compared to 4.4% of TPC patients.

Table 75: Shift Table of Sodium Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - Sodium									
	Eribulin					TPC				
	0	1	2	3	4	0	1	2	3	4
0	291	136	2	11	10	155	46	3	6	3
1	7	23	1	6	5	8	4	0	1	0
2	0	0	0	0	0	1	0	1	0	0
3	0	2	0	0	3	0	0	0	3	2
4	0	0	0	0	2	0	0	0	0	2

Thirty three subjects in the eribulin group developed Grade 3 or 4 hyponatremia and 18 subjects developed grade 3 or 4 hypernatremia at least once during therapy. 28 subjects (5.7%) had Grade 0 or 1 baseline serum sodium levels and developed Grade 3 or 4 hyponatremia during eribulin treatment. Review of the laboratory data revealed that the episodes of hyponatremia were often transient, but persisted in several cases. Review of available case reports revealed one case in which the patient had pre-existing renal insufficiency, one case in which the patient developed acute renal failure which resolved on therapy, and two cases in which the patient was on diuretics during the period of hyponatremia.

SIADH can occur in the setting of malignancies, but is less commonly associated as a paraneoplastic syndrome in breast cancer compared with some other malignancies. However, there have been rare reports of SIADH in association with other microtubule inhibitors; the package inserts for vincristine and vinorelbine include information regarding hyponatremia occurring with or without SIADH, and rare case reports of SIADH in association with vinblastine and docetaxel have been published.

Comment: The incidence of Grade 3 and 4 sodium abnormalities were comparable in the eribulin and TPC groups, and abnormalities tended to be transient. In addition, many of the Grade 3 and 4 abnormalities occurred in patients receiving concomitant medications, such as diuretics, that may have contributed to the sodium abnormalities. However, sodium abnormalities (SIADH) have been rarely associated with other microtubule inhibitors (vincristine and vinblastine) and malignant processes; Assessments for SIADH, including urine electrolytes and serum and urine osmolality, were not monitored during the study. There is insufficient information at this time to make a determination regarding whether eribulin causes sodium abnormalities.

Potassium

The lower limit of normal in the laboratory datasets submitted was 3.5 mmol/L and the upper limit of normal was 5 mmol/L. In study 305, 20 (4%) eribulin-treated subjects experienced potassium abnormalities with a maximum toxicity Grade of 3 (<3 mmol/L or > 6 mmol/L) and 9 (2%) subjects experienced potassium abnormalities (<2.5 mmol/L or > 7 mmol/L) with a maximum of Grade 4. This was comparable to the TPC group, in which potassium abnormalities with a maximum Grade of 3 and 4 were reported in 10 (4%) and 4 (2%) patients, respectively. Among patients with Grade 0 or 1 baseline potassium levels, potassium abnormalities with maximum Grades of either 3 or 4 were reported in 5% of patients in the eribulin group, compared to 6% of TPC patients.

Table 76: Shift Table of Potassium Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - Potassium									
	Eribulin					TPC				
	0	1	2	3	4	0	1	2	3	4
0	237	181	12	15	5	152	41	5	9	2
1	3	28	5	5	1	6	13	2	1	1
2	1	0	1	0	1	0	0	0	0	0
3	0	0	0	0	2	0	0	0	0	0
4	0	1	0	0	0	1	1	0	0	1

Five subjects in the eribulin group developed Grade 4 hyperkalemia and 3 subjects developed Grade 3 hyperkalemia in the eribulin group. A total of 24 eribulin-treated subjects developed Grade 3 or 4 hypokalemia. In all but 6 cases, Grade 3 or 4 potassium abnormalities were transient; in one case, the patient had Grade 3 potassium abnormalities at baseline.

Comment: The incidence of Grade 3 and 4 potassium abnormalities were comparable in the eribulin and TPC groups, and abnormalities tended to be transient. The causes of the potassium perturbations could not be determined from these data: A total of 6% of eribulin-treated patients received furosemide and 9% of eribulin-treated patients received potassium supplementation during the study.

Glucose

Glucose levels were not routinely monitored after the baseline visit. The only abnormalities included in the dataset occurred at the screening visit.

Because glucose serum glucose was not monitored routinely after the initiation of therapy, an association between eribulin and clinically significant glucose abnormalities cannot be ruled out.

Calcium

The lower limit of normal in the laboratory datasets submitted was 8.6 mg/dL and the upper limit of normal was 10 mg/dL. In study 305, 8 (2%) eribulin-treated subjects experienced calcium abnormalities with a maximum toxicity Grade of 3 (< 7 mg/dL or > 12.5 mg/dL) and 17 (3%) experienced calcium abnormalities (< 6 mg/dL or > 13.5 mg/dL) with a maximum toxicity Grade of 4. This was comparable to the TPC group, in which calcium abnormalities with maximum toxicity Grades of 3 and 4 occurred in 8 (2%) and 7 (3%) patients, respectively.

Table 77: Shift Table of Calcium Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - Calcium									
	Eribulin					TPC				
	0	1	2	3	4	0	1	2	3	4
0	243	120	58	7	12	142	38	14	2	5
1	8	23	8	1	0	7	8	5	1	0
2	0	3	4	0	3	0	0	3	1	0
3	0	0	0	0	0	0	1	0	0	1
4	1	0	0	0	2	0	1	0	0	1

A total of 94 patients experienced hypercalcemia of any toxicity grade, and Grade 3 or 4 hypercalcemia occurred in 7 (1%) eribulin-treated patients with Grade 1 or 0 calcium measurements at baseline. A total of 171 patients experienced hypocalcemia of any toxicity grade, and 15 (3%) eribulin-treated patients with baseline calcium levels of Grade 2 or less experienced Grade 3 or 4 hypocalcemia.

Comment: The per-patient incidence of calcium abnormalities was similar in the two treatment groups. Hypercalcemia is common in metastatic disease, and hypocalcemia can result from the treatment of skeletal metastases with bisphosphonates (7% of eribulin patients and 6% of TPC patients received zoledronic acid while on study). In addition, pseudohypocalcemia cannot be ruled out because serum albumin was not routinely monitored.

Magnesium

The laboratory datasets submitted by Eisai assigned a normal range for magnesium of 0.95- 0.725 mmol/L. Table 78 shows shifts in magnesium values for patients who had a baseline lab result and at least one post-baseline result as derived from the ADLB datasets. Of patients with Grade 0 or 1 magnesium levels at baseline, magnesium abnormalities of ≥ Grade 3 toxicity occurred in 5 percent of patients in each treatment group.

Supplemental magnesium was administered to 4% of patients in the eribulin group and 2% of patients in the TPC group. Grade 2 or higher hypomagnesemia was reported in 16 (3.5%) eribulin-treated patients that had Grade 0 or 1 baseline levels. Grade 4 hypomagnesemia was reported in one patient and Grade 3 hypomagnesemia was reported in 4 patients. 14 (3%) eribulin-treated patients with baseline 0 or 1 levels experienced Grade 3 hypermagnesemia and one (0.2%) patient experienced Grade 4 hypermagnesemia. Review of the laboratory data for patients with Grade 2 and above elevations revealed that the vast majority of abnormalities were transient.

Table 78: Shift Table of Magnesium Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - Magnesium									
	Eribulin					TPC				
	0	1	2	3	4	0	1	2	3	4
0	240	145	4	14	2	100	41	1	2	1
1	5	35	4	5	0	5	13	3	1	0
2	0	0	0	0	0	0	0	1	0	0
3	1	1	0	0	0	0	0	0	0	0
4	0	1	0	0	0	0	0	0	0	0

In conclusion, clinically significant hypo- or hypermagnesemia occurred uncommonly, and the incidence of Grade 3 and 4 abnormalities was comparable in the treatment groups. Based upon review of laboratory data in Study 305, there is no clear signal that eribulin causes clinically significant abnormalities in serum magnesium levels in breast cancer patients.

Phosphorus

The datasets assigned a normal range of 0.77-1.52 mmol/L for phosphorus. Table 79 shows shifts in phosphorus values for patients who had a baseline and at least one post-baseline result as derived from the ADLB datasets. Of patients with Grade 0 or 1 phosphorus levels at baseline, Grade 3 and above abnormalities occurred at least once in 6% of patients in the eribulin group (27 of 444 patients) and 2% percent of patients in the TPC group (4 of 170 patients).

Orally administered supplemental phosphorus was minimally used in either treatment group. Grade 2 or higher hypophosphatemia was reported in 81 (18%) eribulin-treated patients that had Grade 0 or 1 baseline levels. Grade 4 hypophosphatemia was reported in five (1%) patients and Grade 3 hypophosphatemia was reported in 22 (5%) patients. All but six of the patients with Grade 3 hypophosphatemia improved to Grade 2 or less, and 4 of the five patients with Grade 4 hypophosphatemia resolved.

Table 79: Shift Table of Phosphorus Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - Phosphorus									
	Eribulin					TPC				
	0	1	2	3	4	0	1	2	3	4
0	342	13	60	22	5	144	5	15	4	0
1	2	0	0	0	0	1	0	1	0	0
2	5	0	2	4	0	0	1	0	0	0
3	1	0	1	1	0	0	0	1	0	0

The etiology of hypophosphatemia occurring in patients in study 305 is likely to be multifactorial. Potential causes of hypophosphatemia include: use of steroids, diuretics, and bisphosphonates; inadequate intake; and decreased intestinal absorption caused by frequent diarrhea. It is possible that increased renal excretion contributed to hypophosphatemia in some cases, but it is unlikely to have been a major factor because renal toxicity did not occur commonly in this population (see the section regarding SAEs, common adverse events and creatinine measurements). However, urine electrolytes were not routinely measured in this study. Dexamethasone was commonly administered to patients in both treatment arms (38% of eribulin patients and 34% of TPC patients). In addition, 7% of eribulin patients and 10% of TPC patients received either furosemide or hydrochlorothiazide, and 7% of eribulin patients and 6% of TPC patients received zoledronic acid.

Creatinine

The lower limit of normal in the laboratory datasets submitted was 53.0 µmol/L (0.6 mg/dL) and the upper limit of normal was 123.8 µmol/L (1.4 mg/dL). Elevations in creatinine occurred rarely in study 305. Among eribulin-treated patients, 5 experienced creatinine elevations with a maximum toxicity Grade of 2 (1.0%), and creatinine elevations maximally graded as 3 and 4 were reported in 3 patients each (0.6%). Grade 3 creatinine elevations occurred in 1.2% of patients in the TPC group, and no Grade 4 creatinine elevations were observed.

Table 80: Shift Table of Creatinine Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - Creatinine									
	Eribulin					TPC				
	0	1	2	3	4	0	1	2	3	4
0	427	40	2	2	3	205	15	2	1	0
1	3	19	2	0	0	4	10	2	1	0
2	0	0	1	1	0	0	0	3	1	0
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0

Review of the detailed laboratory listings showed that 2 of 5 of the Grade 2 creatinine elevations, 1 of the 3 Grade 3 creatinine elevations, and 2 of 3 Grade 4 creatinine elevations normalized or improved to Grade 1 levels. Two of the persistent Grade 3 creatinine elevations occurred in a patient who died of sepsis, and the unresolved Grade 4 creatinine elevation occurred in a diabetic patient who died due to diabetic ketoacidosis.

Table 81 illustrates the mean and median creatinine values by visit for study 305 by cycle. A transient upward trend was noted between cycle 22 and 23; however, only 3 patients had creatinine measured during this cycle and mean and median creatinine measurements returned to the prior level during the subsequent cycle.

Table 81: Mean and Median Creatinine by Number of Cycles

Cycle Number	Number of Patients	Mean Creatinine (µmol/L)	Median creatinine (µmol/L)
1	501	67.7	66.3
2	484	67.8	66.3
3	428	68.0	67.1
4	329	68.5	68.1
5	296	69.1	68.1
6	247	68.9	69.0
7	186	69.3	69.0
8	162	68.0	67.6
9	129	70.5	70.7
10	97	70.0	70.7
11	76	70.7	70.7
12	57	69.2	70.0
13	47	69.2	68.2
14	37	70.1	70.7
15	28	64.9	62.0
16	21	65.9	64.0
17	11	65.2	65.1
18	9	69.0	63.7
19	8	66.0	65.5
20	8	64.8	61.9
21	4	64.8	58.3
22	3	80.3	84.0
23	2	67.5	58.0

In summary, there were rare instances of severe renal adverse events in eribulin-treated patients (as can be expected in a patient population with advanced cancer). However, the majority of cases were transient. Both of the persistent Grade 3 creatinine elevations occurred in the setting of fatal septic shock. The only persistent

Grade 4 elevation occurred during a fatal episode of diabetic ketoacidosis in a patient with a prior history of Type 2 diabetes mellitus. Furthermore, the mean and median creatinine levels do not appear to increase with the number of cycles of eribulin therapy received.

Comment: Based upon review of data from Study 305, this reviewer concludes that there is insufficient evidence to link renal toxicity and eribulin.

ALT

The datasets assigned a normal range for ALT of 14-63 U/L. Table 82 shows shifts in ALT values for patients who had both a baseline lab result and at least one post-baseline result as derived from the ADLB datasets.

Baseline Grade 1 or 2 ALT elevations were present in 25% and 23% of patients in the eribulin and TPC groups, respectively. There were no Grade 4 ALT elevations reported during Study 305 in either treatment group, and the incidence of Grade 3 ALT elevations was low in both treatment arms (3% in the eribulin group and 2% in the TPC group). Among patients with Grade 0 or 1 ALT levels at baseline, 18% of eribulin-treated patients experienced Grade 2 or greater ALT elevations, compared to 12% of patients in the control group.

Comment: Based upon the 6% increase in ≥ Grade 2 ALT elevations in patients with Grade 0 or 1 levels at baseline observed in the eribulin group, the following text was added to the Adverse Reactions Section of the proposed label:

Liver Function Test Abnormalities: Among patients with Grade 0 or 1 ALT levels at baseline, 18% of eribulin-treated patients experienced Grade 2 or greater ALT elevation, compared to 12% of patients in the control group. One eribulin-treated patient without documented liver metastases had concomitant Grade 2 elevations in bilirubin and ALT; however, these abnormalities resolved despite rechallenge with eribulin.

Table 82: Shift Table of ALT Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - ALT									
	Eribulin Arm					TPC Arm				
	0	1	2	3	4	0	1	2	3	4
0	189	143	37	3	0	109	56	13	0	0
1	2	61	38	8	0	7	28	12	3	0
2	0	3	10	5	0	0	2	3	2	0

Table 83 illustrates the mean and median ALT values by visit for study 305 by cycle. There does not appear to be a trend in median or mean ALT values over the course of eribulin therapy.

Table 83: Mean and Median ALT by Number of Cycles

Cycle Number	Number of Patients	Mean ALT (U/L)	Median ALT (U/L)
1	501	47	36
2	484	39	31
3	428	35	30
4	329	37	28
5	296	38	29
6	247	37	30
7	186	37	29
8	162	34	27
9	129	35	28
10	97	31	26
11	76	28	24
12	57	27	24
13	47	26	25
14	37	27	24
15	28	29	22
16	21	26	25
17	11	29	29.5
18	9	26	17
19	8	28	20
20	8	23	18
21	4	33	22
22	3	25	23
23	2	30	27

AST

The datasets assigned a normal range for AST of 6-33 U/L. Table 84 shows shifts in AST values for patients who had a baseline lab result and at least one post-baseline result as derived from the ADLB datasets.

There was one Grade 4 AST elevation (0.2% of patients) in the eribulin group during study 305, and no Grade 4 AST elevations in the TPC group. The percentage of patients who experienced grade 3 AST levels at least once was comparable in the treatment arms (5% in both the eribulin and TPC groups, respectively). Among patients with Grade 0 or 1 AST levels at baseline, 16% of eribulin-treated patients

experienced AST elevations with maximum toxicity grades of 2, compared to 11% of patients in the control group. The percentage of patients with baseline AST levels of 0 or 1 who developed AST elevations with a maximum toxicity Grade of 3 was comparable in the two groups (2% in the eribulin group and 3% in the TPC group). The Grade 1 AST elevations were common in both treatment groups (48% in the eribulin group and 47% in the TPC group). However, 32% of eribulin-treated patients and 36% of TPC-treated patients had Grade 1 AST measurements at baseline.

Table 84: Shift Table of AST Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - AST									
	Eribulin Arm					TPC Arm				
	0	1	2	3	4	0	1	2	3	4
0	128	146	22	3	0	71	60	3	1	0
1	6	96	54	6	0	9	53	21	5	0
2	0	0	18	14	1	0	2	5	5	0
3	0	0	0	3	0	0	0	0	1	0

Table 85 illustrates the mean and median AST values by visit for study 305 by cycle. There does not appear to be a positive trend in median or mean AST values over the course of eribulin therapy.

Table 85: Mean and Median AST by Number of Cycles

Cycle Number	Number of Patients	Mean AST (U/L)	Median AST (U/L)
1	501	48	38
2	484	42	34
3	428	39	33
4	329	40	32
5	296	40	32
6	247	39	33
7	186	39	32
8	162	35	30
9	129	36	30
10	97	33	29
11	76	32	28
12	57	33	30
13	47	33	27
14	37	34	25
15	28	33	23
16	21	32	24
17	11	27	25

Cycle Number	Number of Patients	Mean AST (U/L)	Median AST (U/L)
18	9	25	24
19	8	27	25
20	8	25	25
21	4	28	27
22	3	28	29
23	2	32	32

In summary, AST abnormalities were common in both treatment arms, but Grade 3 and above AST toxicities were relatively infrequent. Given that liver metastases were present in 60% of patients enrolled in Study 305, it is unclear to what degree eribulin contributed to this finding. No Hy's law cases were apparent in the data review of Study 305. *Based on the data and the high prevalence of liver metastases, it cannot be determined what contribution, if any, that eribulin caused liver toxicities occurred.*

Bilirubin

The datasets assigned a normal range for bilirubin of 5-21 µmol/L. Table 86 shows shifts in bilirubin values for patients who had a baseline and at least one post-baseline result as derived from the ADLB datasets.

There were no Grade 4 bilirubin measurements in either treatment group, and the incidence of Grade 3 bilirubin levels was low in both treatment arms (1% in the eribulin group and 2% in the TPC group). Grade 2 bilirubin abnormalities were also comparable (4% in the eribulin group compared to 5% in the TPC group).

Table 86: Shift Table of Bilirubin Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - Bilirubin							
	Eribulin Arm				TPC Arm			
	0	1	2	3	0	1	2	3
0	418	46	13	4	183	29	8	3
1	4	5	6	1	2	3	3	0
2	0	0	1	0	0	0	1	2

Table 87 illustrates the mean and median bilirubin values by visit for study 305 by cycle. There does not appear to be a positive trend in median or mean bilirubin values over the course of eribulin therapy.

Table 87: Mean and Median Bilirubin by Number of Cycles

Cycle Number	Number of Patients	Mean Bilirubin (µmol/L)	Median Bilirubin (µmol/L)
1	501	9	9
2	484	9	9
3	428	10	9
4	329	10	9
5	296	10	9
6	247	10	9
7	186	9	9
8	162	9	9
9	129	9	9
10	97	9	9
11	76	9	9
12	57	9	9
13	47	9	9
14	37	10	9
15	28	9	9
16	21	10	9
17	11	9	9
18	9	8	9
19	8	8	9
20	8	7	8
21	4	10	10
22	3	8	8
23	2	8	7

In summary, clinically significant bilirubin elevation was uncommon in both treatment arms.

Alkaline Phosphatase (ALP)

The datasets assigned a normal range of 28-94 U/L for ALP. Table 88 shows shifts in ALP values for patients who had a baseline and at least one post-baseline result as derived from the ADLB datasets.

Ten percent of eribulin patients and 6% of TPC patients had Grade 2 or 3 ALP measurements at baseline. There were no Grade 4 ALP measurements reported in either treatment group during Study 305, and the incidence of Grade 3 ALP measurements was comparable (5% in the eribulin group 3% in the TPC group). Grade 2 ALP measurements were also similar (12% in the eribulin group compared to 11% in the TPC group).

Table 88: Shift Table of ALP Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - ALP							
	Eribulin Arm				TPC Arm			
	0	1	2	3	0	1	2	3
0	195	98	7	1	79	55	2	0
1	10	107	23	7	2	64	16	3
2	0	1	27	15	0	2	8	1
3	0	0	2	4	0	0	0	3

Table 89 illustrates the mean and median ALP values by visit for study 305 by cycle. There does not appear to be a positive trend in median or mean ALP values with increasing cycles of eribulin therapy. An upward trend was noted after cycle 21. However, only 6 patients had ALP measured during these cycles.

Table 89: Mean and Median ALP by Number of Cycles

Cycle Number	Number of Patients	Mean ALP ($\mu\text{mol/L}$)	Median ALP ($\mu\text{mol/L}$)
1	1033	150	106
2	1359	149	106
3	1112	141	102
4	848	142	101
5	761	147	97
6	627	144	96
7	485	148	94
8	420	131	93
9	335	134	100
10	250	124	97
11	199	116	90
12	154	112	101
13	127	119	110
14	99	121	104
15	75	127	108
16	60	124	106
17	30	101	85
18	24	91	71
19	21	85	77
20	21	90	75
21	11	93	79
22	6	136	150
23	6	144	131

Grade 1 and 2 ALP abnormalities were common at baseline and during study treatment in both the eribulin and TPC groups. Grade 3 ALP elevations were less common, and were comparable in the two groups. The most likely cause of ALP abnormalities in the study was metastatic disease, particularly bone and liver metastases. Based upon the available data, there is insufficient information to establish causality.

Hy's Law

The July 2009 FDA industry guidance document entitled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” states that the “most specific predictor found to date of a drug’s potential for severe hepatotoxicity.... is the occurrence of a small number of cases of hepatocellular injury (aminotransferase elevation) accompanied by increased serum total bilirubin, not explained by any other cause.” The guidance document describes 3 components to Hy’s Law, which designates drugs likely to cause severe drug-induced liver injury:

1. A higher incidence of 3-fold or greater elevations of aminotransferase levels seen with the study drug compared to a nonhepatotoxic control group
2. Among trial subjects showing such aminotransferase levels, one or more also have elevations in total bilirubin > 2 times the upper limit of normal (without findings of cholestasis).
3. Lack of another reason to explain the increased aminotransferase and total bilirubin levels.

Criterion number one is partially fulfilled, in this reviewer’s opinion. The incidence of Grade 2 and above ALT and AST in patients with Grade 0 or 1 ALT elevations at baseline was higher in the eribulin group compared to the control group [ALT: 86 of 481 eribulin-treated patients (18%) and 28 of 229 (12%) TPC patients; AST: 85 of 461 (18%) eribulin patients and 30 of 223 (14%) TPC patients]. However, these results may be confounded by the fact that eribulin-treated patients, in general, remained on study for longer periods of time (the median duration of treatment in the eribulin arm was 118 days compared to 64 days for patients receiving chemotherapy and 34 days for patients receiving hormonal therapy in the TPC group).

This review used a broad search strategy to include all patients with \geq Grade 2 ALT (> 2.5 X ULN) and bilirubin elevations (> 1.5 X ULN) that occurred at the same time-point after initiation of eribulin treatment.

A review of the dataset found two cases meeting Hy’s Law ALT and bilirubin criteria (bilirubin > 2 X ULN and ALT > 3 X ULN). One case occurred in the setting of liver metastases, and the patient continued eribulin therapy with subsequent improvement of transaminase and bilirubin abnormalities to Grade 1 or less. The other patient had transient ALT and bilirubin elevations and continued treatment.

- Patient 25021013 had hepatic metastases, and developed Grade 3 elevations of bilirubin, AST and ALT at the Cycle 4 Day 1 visit. The patient subsequently completed an additional 5 cycles of eribulin therapy at the full dose. At the study termination visit, AST and bilirubin levels were normal and ALT elevation was Grade 1.
- Patient 29081002 had Grade 2 ALT and bilirubin elevations noted at an unscheduled visit during Cycle 7. However, ALT and bilirubin levels subsequently improved to \leq Grade 1 levels prior to the next visit and the patient received an additional one and a half cycles of eribulin therapy before leaving the study due to progressive disease by RECIST. The patient died one month after the last eribulin treatment due to disease progression.

Six additional patients did not meet Hy's Law criteria based upon ALT and bilirubin elevations, but had concomitant AST elevations $> 3 \times$ ULN and bilirubin levels $> 2 \times$ ULN:

- Patient 28121019 had baseline liver metastases and developed Grade 2 elevations in AST, ALT and bilirubin at the Cycle 2, Day 8 visit. Grade 3 AST and Grade 2 bilirubin and ALT elevations were recorded at the study termination visit. The patient was discontinued from the study due to clinical progression and larger liver by palpation. The patient died two and a half months after cessation of treatment due to progressive disease
- Patients 11011003, 13041001 and 19031016 had grade 2 AST and bilirubin elevations but had liver metastases.
- Patient 20041003 had Grade 2 AST and Grade 1 Bilirubin elevations at baseline in addition to liver and lung metastases. Patient had Grade 3 AST and bilirubin levels at study termination, which was due to clinical progression (hepatic progression and increased bilirubin values noted by the investigator in the comments section of the dataset). The patient died 4 months later due to progressive disease.
- Patient 14021004 had had a Grade 1 AST elevation and multiple bone and lung metastases recorded at baseline. Grade 3 bilirubin elevation and Grade 2 AST elevations were recorded at study termination due to progressive disease by RECIST criteria (including multiple new liver lesions). The patient died four months later due to progressive disease.

Three additional patients had concomitant Grade 2 bilirubin and ALT elevations that did not meet Hy's law criteria. Two patients had documented liver metastases:

- Patient 16041007 developed Grade 2 AST and bilirubin elevation at the Cycle 6 day 1 visit. This patient had hepatic metastases that hadn't

- Patient 23031002 had concomitant Grade 2 elevations in Bilirubin and ALT without hepatic metastases at the Cycle 4 Day 15 visit. Patient was subsequently taken off therapy due to disease progression. At the study termination visit, bilirubin and AST levels were normal, and ALT had improved to Grade 1 toxicity levels.
- Patient 29091001 had liver metastases and Grade 2 elevations of bilirubin, AST and ALT at the study termination visit (after 7 cycles of therapy). Patient discontinued therapy due to peripheral neuropathy, asthenia, and anorexia, and died 2 months later due to progressive disease.

In summary, none of the cases identified based upon ALT, AST, and elevations meet all the components of Hy's Law. All but one of the cases occurred in patients with hepatic metastases, and the remaining patient had transient ALT and bilirubin elevations that did not recur despite subsequent eribulin therapy. *Thus, there is no evidence at this time that eribulin causes clinically significant liver injury. However, the following text was added to the adverse reactions section of the label to inform clinicians of the changes in ALT and bilirubin noted in Study 305:*

Liver Function Test Abnormalities: Among patients with Grade 0 or 1 ALT levels at baseline, 18% of eribulin-treated patients experienced Grade 2 or greater ALT elevation, compared to 12% of patients in the control group. One eribulin-treated patient without documented liver metastases had concomitant Grade 2 elevations in bilirubin and ALT; however, these abnormalities resolved despite rechallenge with eribulin.

Urinalysis

Urine specimens were collected for basic urinalyses at Baseline, on Day 1 of each cycle, and at the termination visit for patients randomized to the eribulin arm. Review of urinalysis data was complicated by the fact that the datasets provided by Eisai did not assign normal values for each parameter measured, so every measurement was classified as "normal". In addition, the units of measurement were not consistent among patients for a given parameter measured, and the units for quantitative measurements were often absent.

One patient in the TPC group was identified with clinically significant proteinuria (1 G/L) after baseline. Nineteen subjects were identified in the eribulin group with either 2+ or 3+ proteinuria, or 100 – 300 mg/dl of protein measured. The majority of elevations were transient, but 2+ urinary protein or higher was noted in the study termination visit for 7 patients (and therefore data from any follow up urinalyses that may have been performed for these patients is not available). Twenty-four hour urine collection was not performed in these patients, so conclusions regarding extent of proteinuria and creatinine clearance cannot be drawn.

Review of the datasets identified 2 patients on the eribulin group and 3 patients in the TPC group with potentially clinically significant hematuria that did not improve during the course of the study. 4+ hemoglobin was noted in two eribulin patients; however, they both had abnormal positive urinary hemoglobin at baseline.

In summary, there was no significant safety signal identified from review of the urinalysis data; however, the data could not rule out such a signal.

Hematology

During the conduct of Study 305, hematology labs were to be obtained at screening, Days 1 and 8 of each cycle, on Day 15 of Cycles 1 and 2 (unless \geq Grade 3 neutropenia occurred in Cycle 1 or 2), at the study termination visit, and when clinically indicated for patients randomized to the receive eribulin. Hematologic assessments included: red blood cell count, hemoglobin, hematocrit, platelet count, total white blood cell count with differential, and absolute neutrophil count. The protocol for Study 305 stated that the schedule of laboratory assessments for patients randomized to receive TPC should be based upon standard practices for the chosen treatment. *The lack of uniform assessment of laboratory data during study 305 makes comparison of data between treatment arms difficult; laboratory abnormalities may be underreported (or over-reported) in the TPC arm because the patients in this arm may not have undergone the same number and types of laboratory tests during the course of their treatment.*

Neutrophils

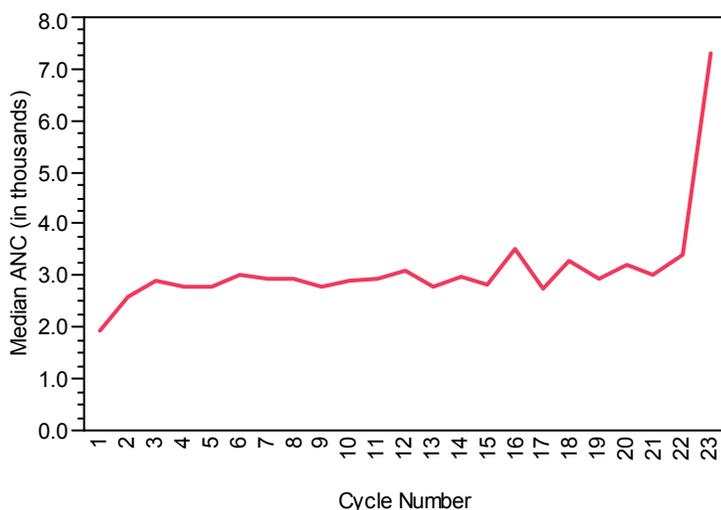
The datasets assigned a normal range of $1.6-7 \times 10^9/L$ for neutrophils. Table 90 shows shifts in Absolute Neutrophil Count (ANC) values for patients who had a baseline and at least one post-baseline result as derived from the ADLB datasets for Study 305. This shift table illustrates that a higher percentage of patients exhibited severe neutropenia in the eribulin group compared to the TPC group. A total of 144 (29%) patients in the eribulin group and 22 (9%) patients in the TPC group experienced Grade 4 neutropenia. A total of 141 (28%) of eribulin treated patients and 35 (14%) of TPC patients experienced neutropenia with a maximum toxicity grade of 3.

Table 90: Shift Table of ANC Levels by CTCAE Grade

Baseline CTCAE Grade	Maximum CTCAE Grade - ANC									
	Eribulin Arm					TPC Arm				
	0	1	2	3	4	0	1	2	3	4
0	87	35	87	138	135	112	35	29	31	21
1	0	1	2	3	7	0	7	3	2	1
2	0	1	0	0	2					
3						0	0	0	1	0
4						0	1	0	0	0

Figure 10 depicts the median ANC for each cycle of eribulin therapy completed. This figure indicates that the median ANC did not seem to be influenced by the number of cycles of eribulin therapy completed (i.e., ANC toxicity does not appear to be cumulative). However, these results may be confounded by the use of granulocyte colony stimulating factors in approximately 19% of eribulin-treated patients in Study 305.

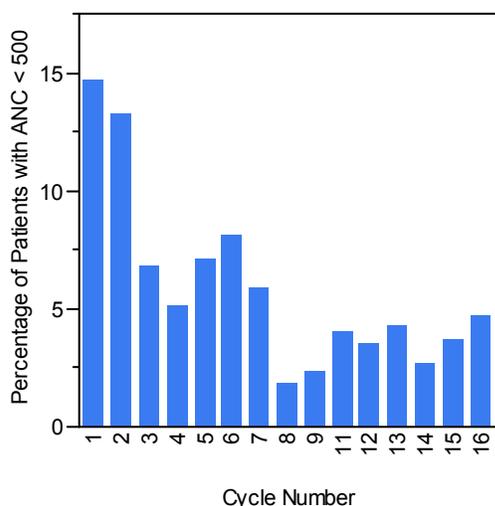
Figure 10: Median ANC by Number of Cycles Completed



Cycle Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Number of Patients	496	482	424	327	295	246	186	161	129	97	74	57	46	37	27	21	11
Cycle Number	18	19	20	21	22	23											
Number of Patients	9	8	8	4	2	2											

Figure 11 illustrates the percentage of patients who developed Grade 4 neutropenia in study 305 for each treatment cycle. In general, it appears that a higher percentage of patients developed Grade 4 neutropenia in the first two cycles of therapy; the percentage of patients with Grade 4 neutropenia appeared to stabilize from cycle 3 onwards. *Comment: This pattern indicates that patients are at highest risk of developing severe neutropenia in the first few cycles of therapy. The decreased risk of neutropenia in subsequent cycles may be due to the use of dose delays, reductions, and granulocyte colony stimulating factors in Study 305.*

Figure 11: Percentage of Patients with Grade 4 Neutropenia in Study 305



Cycle Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Number of neutropenic Patients	73	64	29	17	21	20	11	3	3	0	3	2	2	1	1	1
Number of Patients Assessed	496	482	424	327	295	246	186	161	129	97	74	57	46	37	27	21

Lymphocytes

Analysis of lymphocyte counts was complicated by the fact that the dataset assigned multiple different values for the upper and lower limits of the normal range. The lower limit of normal ranged from 0-7.225 X 10⁹/L and the upper limit of normal ranged from 0.4 to 9.768 X 10⁹/L in the datasets.

A total of 69 of 484 (14%) eribulin-treated patients with normal to Grade 2 lymphocyte counts at baseline developed lymphopenia of Grade 3 or higher severity during study

305. A total of 22 of 236 (9%) patients in the TPC group with normal to Grade 2 baseline lymphocyte counts developed Grade 3 or 4 lymphopenia at least once during the study period. Ten patients (2%) experienced Grade 4 lymphopenia in the eribulin group, compared to 2 (1%) TPC patients. Review of the laboratory data of the 10 patients in the eribulin group with Grade 4 lymphopenia revealed that Grade 4 lymphopenia was transient for 9 of the patients.

Eosinophils

Moderate hypereosinophilia (counts of 1.5 to $5 \times 10^9/L$) occurred infrequently in Study 305 in patients who had normal eosinophil counts at baseline. Patients 19111008 and 19111001 developed transient moderate eosinophilia. In addition, an eosinophil count of $38 \times 10^9/L$ was recorded during the Cycle 2 Day 8 visit for patient 14091005; however, this patient's eosinophil count normalized on the Cycle 3 Day 1 visit and eosinophilia did not recur. *Review of the adverse events recorded for patient 14091005 did not reveal any hypersensitivity or allergy related adverse events.*

Platelets

The datasets assigned a normal range of 100 - $550 \times 10^9/L$ for platelets. Table 91 shows shifts in platelet values for patients who had a baseline and at least one post-baseline result as derived from the ADLB datasets for Study 305. This shift table illustrates that only a small percentage of patients developed severe thrombocytopenia ($< 50 \times 10^9/L$). Two (0.4%) patients in the eribulin group and 4 (1.6%) patients in the TPC group experienced Grade 4 thrombocytopenia. Five (1.0%) of eribulin-treated patients and 2 (0.8%) TPC patients experienced thrombocytopenia with a maximum toxicity grade of 3.

Because Grade 4 thrombocytopenia can be life-threatening, a review of the two eribulin-treated patients who experienced Grade 4 thrombocytopenia was conducted. Patient 15041001 had Grade 4 thrombocytopenia at her cycle 5 day 1 visit. She discontinued eribulin therapy due to this thrombocytopenia, which improved to Grade 2 levels one week later. Patient 28191007 had a platelet count of $6 \times 10^9/L$ when she was hospitalized for febrile neutropenia, stomatitis, and palmar-plantar erythrodysesthesia syndrome 19 days after the Cycle 3, day 8 dose. Platelet counts improved to Grade 2 levels within ten days.

Thrombocytopenia occurs rarely with eribulin. The proposed label contains dose modifications guidelines for thrombocytopenia.

Table 91: Shift Table of Platelets by CTCAE Grade for Study 305

Baseline CTCAE Grade	Maximum CTCAE Grade - Platelets									
	Eribulin Arm					TPC Arm				
	0	1	2	3	4	0	1	2	3	4
0	397	77	5	4	2	170	48	3	2	2
1	3	10	0	1	0	3	10	3	0	2

Hemoglobin

The datasets assigned a normal range of 120-170 g/L for hemoglobin. Table 92 shows shifts in hemoglobin values for patients who had a baseline and at least one post-baseline result as derived from the ADLB datasets for Study 305. This shift table illustrates that a only a small percentage of patients developed severe anemia (< 80 g/L). Two (0.4%) patients in the eribulin group and no patients in the TPC group experienced Grade 4 anemia. Ten (2%) eribulin-treated patients and 10 (4%) TPC patients experienced Grade 3 anemia.

Table 92: Shift Table of Hemoglobin by CTCAE Grade for Study 305

Baseline CTCAE Grade	Maximum CTCAE Grade - Hemoglobin									
	Eribulin Arm					TPC Arm				
	0	1	2	3	4	0	1	2	3	4
0	107	186	22	2	1	65	70	21	3	0
1	3	87	68	4	1	2	37	34	6	0
2	0	2	13	4	0	0	0	4	1	0

Comment: The proposed label indicates that anemia of any Grade was experienced by ^{(b) (4)} of eribulin treated patients, and that Grade 3 and above anemia was reported in 2% of patients.

7.4.3 Vital Signs

Temperature, blood pressure and heart rate were measured at screening, Days 1 and 8 of each cycle, Day 15 of Cycles 1 and 2, at study termination, and when deemed necessary. Weight measurements were recorded at screening, Day 1 of each cycle, and at study termination.

Temperature elevation:

A total of 15 patients developed a temperature of ≥ 38 degrees Celsius that was recorded during Study 305. Thirteen patients had temperatures between 38 °C and 39 °C, and the remaining two patients had temperatures of 39 °C. *Comment: the proposed label includes the preferred term “pyrexia”, which was reported in 21% of eribulin-treated patients in Study 305 (all Grade 2 or below).*

Hypotension:

In Study 305, hypotension occurred with equal frequency in the two treatment groups. Thirty (6%) patients in the eribulin group and 14 (6%) patients in the TPC group experienced a systolic blood pressure less than 90 mm Hg.

Hypertension:

A total of 91 (18%) patients in the eribulin group and 41 (17%) patients in the TPC group experienced at least one episode of hypertension with a systolic blood pressure (SBP) > 150 mmHg. Of the 91 eribulin-treated patients with hypertension, 19 (21%) had a SBP greater than 150 mm/Hg at baseline. Of the 41 patients in the TPC group, 13 (32%) were hypertensive at baseline. Investigators reported hypertension-related treatment-emergent adverse events for 8 (1.6%) patients in the eribulin group.

7.4.4 Electrocardiograms (ECGs)

In Study 305, ECG evaluations were performed at screening and at Study Termination for all patients. Patients randomized to receive eribulin had an additional ECG prior to commencement of the second cycle of eribulin.

Four patients (0.8%) in the eribulin group and two patients (0.8%) in the TPC group had ECG abnormalities that were clinically significant at the study termination visit. One of the four eribulin-treated patients with abnormal ECGs also had a significant ECG abnormality at baseline. The following patients had normal ECGs or ECGs with minor abnormalities but had significant ECG abnormalities at study termination:

- An ECG for patient 23021005 demonstrated ST depression in the anterior leads. Hypertension was reported 5 days after her first eribulin infusion and atrial tachycardia was reported ten days after her first dose of eribulin. This patient only had a single dose of eribulin mesylate prior to discontinuation from study therapy due to fatal meningeal metastases.
- An ECG for patient 28151010 was concerning for probably left ventricular hypertrophy. This patient did not have cardiac adverse events during the study
- The ECG for patient 28151015 demonstrated diffuse low voltage. No cardiac adverse events were reported for this patient.

In the integrated summary of safety, which included all 1,222 patients treated with eribulin, two cases of arrhythmia, two cases of first degree heart block, one case of atrial fibrillation and one case of supraventricular tachycardia were reported. No events of Torsade de Pointes were reported in eribulin-treated subjects. In study 211, one patient died of cardiac arrest over 30 days after receipt of the last eribulin dose. An additional subject died unexpectedly due to an “unknown” cause five days after

receipt of eribulin. This patient was on multiple concomitant medications at the time of the event.

In conclusion, the existing data do not contain reports of significant ventricular arrhythmias or Torsades de Pointes; however, an effect on QTc intervals was observed in the dedicated QT study. A warning regarding increased QTc intervals following eribulin exposure was recommended by clinical pharmacology and clinical review team members. Definitive conclusions regarding the cause of the two reported cases of sudden death cannot be made due to the lack of ECG data recorded at the time of the events and confounding comorbid conditions and concomitant medications.

7.4.5 Special Safety Studies/Clinical Trials

Please see Section 4.4.4 for a summary of QTIRT review of the dedicated QT study E7389-E044-110.

7.4.6 Immunogenicity

Immunogenicity studies were not conducted for eribulin.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A formal analysis of dose dependency for adverse events was not possible. All patients in Study 305 were treated with a uniform dose of eribulin, unless dose delays and reductions were required due to adverse events.

7.5.2 Time Dependency for Adverse Events

Please see Section 7.3.5 of this review for a discussion of the time-dependency of peripheral neuropathy adverse events, and section 7.4.2 for an analysis of the time-dependency of severe neutropenia.

7.5.3 Drug-Demographic Interactions

Race

Because 93% of patients in the eribulin group in Study 305 were classified as White, explorations of difference in adverse events based on race would not be informative. In the integrated summary of safety, 83% of breast cancer patients were White and 8% of breast cancer patients did not have a race classification recorded. Therefore, an analysis of the effect of race on adverse events occurring in this population would also

not be fruitful. The applicant analysis indicated that “no notable differences in the overall incidence of TEAEs by race” in the all eribulin treated (N=1222) and breast cancer (N=827) populations.

Gender

Because all breast cancer studies included in the integrated summary of safety enrolled only female subjects, analysis of adverse events by gender is not possible.

Age

Study 305 was the only study with a control arm submitted with this application. In Study 305, 93 (43%) patients who received eribulin were greater than or equal to 65 years of age. Because the total number of patients ≥ 65 years of age was less than 100 in Study 305, no definitive conclusions can be made regarding the safety of eribulin in older patients. Table 93 shows an exploratory analysis of adverse events by MedDRA SOC in patients 65 years or older compared to patients younger than 65. The incidence of adverse events in both groups was similar. No SOC had a $\geq 10\%$ difference in adverse event incidence.

Table 93: Comparison of Adverse Events by MedDRA SOC in Patients ≥ 65 Years of Age in Study 305

Adverse Event Term by MedDRA SOCs	All Grades %		Grades 3 and Above %	
	≥ 65 (N = 94)	< 65 (N=409)	≥ 65 (N = 94)	< 65 (N=409)
Blood And Lymphatic System Disorders	63	61	55	48
Cardiac Disorders	7	6	0	1
Ear And Labyrinth Disorders	10	8	1	0
Endocrine Disorders	1	0	0	0
Eye Disorders	20	15	0	0
Gastrointestinal Disorders	55	63	3	5
General Disorders And Administration Site Conditions	74	68	21	12
Hepatobiliary Disorders	6	6	0	2
Immune System Disorders	1	2	0	0
Infections And Infestations	40	42	5	6
Injury, Poisoning And Procedural Complications	11	4	2	0
Investigations	38	36	7	5
Metabolism And Nutrition Disorders	36	34	11	6
Musculoskeletal And Connective Tissue Disorders	55	52	7	5

Adverse Event Term by MedDRA SOCs	All Grades %		Grades 3 and Above %	
	≥ 65 (N = 94)	< 65 (N=409)	≥ 65 (N = 94)	< 65 (N=409)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	9	7	2	3
Nervous System Disorders	53	61	14	11
Psychiatric Disorders	17	20	2	1
Renal And Urinary Disorders	10	6	1	0
Reproductive System And Breast Disorders	3	3	0	1
Respiratory, Thoracic And Mediastinal Disorders	45	36	12	5
Skin And Subcutaneous Tissue Disorders	48	54	1	1
Surgical And Medical Procedures	0	0	0	0
Vascular Disorders	21	15	1	2

Table 94 lists adverse events by MedDRA preferred term that occurred with a per-patient incidence rate of 5% or higher in patients who were ≥ 65 years of age (shaded entries indicate a ≥ 5% increased incidence of adverse events in the ≥ 65 age group). Overall, the incidence rates were comparable in the two patient populations. The largest positive discrepancy in the incidence of adverse events of all grades in the elderly was observed for the preferred terms of peripheral edema (a 12% difference in the per-patient incidence rate), followed by asthenia (9% difference), and anemia (9% difference). Among adverse events of Grade 3 and higher severity, the largest positive discrepancy was reported for neutropenia (8% discrepancy), asthenia (8%) and dyspnea (7%).

No grade 5 neutropenia events occurred in either population. Of the patients aged 65 years of age or older, 25 experienced grade 4 neutropenia and 24 experienced grade 3 neutropenia. This did not result in a higher percentage of infections (note SOC of infections and infestations comparable between two age groups). Twelve patients had grade 3 asthenia in the 65 and older subset (no grade 4 or above). 8 elderly patients had grade 4 dyspnea, and one suffered a grade 5 dyspneic event.

Table 94: Comparison of Adverse Events by MedDRA Preferred Term in Patients ≥ 65 Years of Age in Study 305

Adverse Event Term by MedDRA Preferred Term	All Grades %		Grades 3 and Above %	
	≥ 65 (N = 94)	< 65 (N=409)	≥ 65 (N = 94)	< 65 (N=409)
Neutropenia	57	50	52	44
Alopecia	41	45	0	0
Asthenia	36	25	13	5
Fatigue	30	29	6	3
Anemia	26	17	2	2
Nausea	26	37	1	1
Weight Decreased	24	21	1	1
Constipation	23	25	1	1
Leukopenia	23	23	16	13
Diarrhea	21	18	0	0
Anorexia	20	19	1	0
Dyspnea	20	15	10	3
Arthralgia	19	12	0	0
Back Pain	19	15	0	1
Peripheral Edema	19	7	0	0
Pyrexia	18	22	0	0
Bone Pain	17	11	4	1
Cough	15	14	0	0
Paresthesia	14	11	1	2
Abdominal Pain Upper	12	8	0	0
Pain In Extremity	12	11	0	1
Dyspepsia	11	8	0	0
Lacrimation Increased	11	6	0	0
Urinary Tract Infection	11	10	1	1
Vomiting	11	20	1	1
Headache	10	22	0	0
Mucosal Inflammation	10	8	1	1
Myalgia	10	11	0	0
Peripheral Sensory Neuropathy	10	13	2	2
Dizziness	9	7	0	1
Muscular Weakness	9	5	2	0
Neuropathy Peripheral	9	8	2	2
Upper Respiratory Tract Infection	9	4	0	0
Neuropathy	7	4	3	1
Pharyngolaryngeal Pain	7	7	1	0
Stomatitis	7	8	1	0

Adverse Event Term by MedDRA Preferred Term	All Grades %		Grades 3 and Above %	
	≥ 65 (N = 94)	< 65 (N=409)	≥ 65 (N = 94)	< 65 (N=409)
Dysgeusia	6	8	0	0
Hypokalemia	6	7	3	2
Hypomagnesaemia	6	4	1	0
Musculoskeletal Chest Pain	6	7	0	0
Dry Mouth	5	6	0	0
Dry Skin	5	1	0	0
Gastroesophageal Reflux Disease	5	2	0	0
Hypertension	5	3	0	0
Insomnia	5	8	0	0
Vertigo	5	4	1	0

Comment: Based upon these exploratory analyses, there does not appear to be a substantially increased incidence of clinically relevant adverse events associated with eribulin therapy in the elderly population.

Among all 1,222 patients treated with eribulin, 244 subjects were > 65 years of age. The applicant-conducted analyses of adverse events in this population indicated that toxicities did not occur more frequently in the elderly population.

7.5.4 Drug-Disease Interactions

Please see Section 4.4.3 of this review for a discussion of the effects of hepatic and renal impairment on eribulin pharmacokinetics. Section 7.3.5 of this review provides a discussion of serious treatment emergent adverse events and neutropenia in patients with hepatic impairment.

7.5.5 Drug-Drug Interactions

The applicant conducted an analysis of the effects of concomitant CYP3A4 inhibitors and inducers on the incidence of adverse events in all eribulin treated patients (N=1222) and in all patients with breast cancer who received the targeted dose of eribulin (N=827). This analysis demonstrated a trend for a higher percentage of serious treatment-emergent adverse events, febrile neutropenia, and adverse events leading to treatment discontinuation, delay, or reduction in patients taking concomitant CYP3A4 inhibitors. However, the most commonly used CYP3A4 inhibitors were anti-fungal and anti-bacterial agents, and patients receiving such medications may have had a higher predisposition to infections.

Comment: Study 109 demonstrated that the CYP3A4 inducer ketoconazole did not affect eribulin pharmacokinetics. Therefore, there is uncertainty as to whether the increased incidence of adverse events observed in patients taking concomitant CYP3A4 inhibitors is related to the effects of these inhibitors on eribulin pharmacokinetics, or whether it is due to other confounding factors.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies have not been conducted with eribulin. Eribulin was not mutagenic in an *in vitro* bacterial reverse mutation assay (Ames test). Mutagenicity was observed in mouse lymphoma mutagenesis assays, and eribulin was clastogenic in an *in vivo* rat bone marrow micronucleus assay.

7.6.2 Human Reproduction and Pregnancy Data

There are no clinical studies of Halaven in pregnant or lactating women. Such studies are usually not required for drugs intended to treat patients with advanced cancer. In the proposed label, Halaven is designated as Pregnancy Category “D” based upon findings of embryofetal toxicity and teratogenicity animal studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

Studies with safety data pertaining to pediatric patients were not submitted with this NDA. Eisai requested a full waiver of the requirements for pediatric use studies under the Pediatric Research Equity Act. The Pediatric Review Committee (PeRC) granted this waiver because the rarity of breast cancer in the pediatric population (0-18) renders conduct of the necessary studies impossible or highly impracticable.

Comment: This reviewer concurs with the PeRC that a waiver of the requirements under the Pediatric Research Equity Act is warranted. A recent article in J Surg Res 2008 June 15;147(2) by Gutierrez JC et al identified only 75 patients 19 years old and younger with malignant breast tumors diagnosed between 1973 and 2004 from the SEER database.

Section 8.3 of the proposed label indicates that the safety and effectiveness of Halaven in pediatric patients below the age of 18 years have not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no expected drug abuse potential for eribulin. The integrated summary of safety included a report of one patient enrolled in Study 301 who received approximately 4 times the recommended dose of eribulin on Cycle 2 Day 1. This patient experienced a Grade 3 hypersensitivity reaction on Day 3 that resolved within one day with steroid and antihistamine treatment and Grade 3 neutropenia that lasted seven days. There is no known antidote for an eribulin overdose.

There is no data regarding whether cessation of eribulin therapy results in signs or symptoms of withdrawal or rebound.

7.6.5 Additional Submissions / Safety Issues

In accordance with 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a 120-day Safety Update Report. This submission included datasets reflecting updated survival data through March 3, 2010, and adverse event and laboratory data through November 30, 2010 for Study 305.

Analysis of Deaths Occurring After Data Cut-Off Date

The ADSL (subject level) dataset included in the 120-day safety update was analyzed to elucidate the causes of death for patients who died between May 13, 2009 and March 3, 2010. The data submitted by the sponsor indicated that 112 additional patient deaths occurred on the eribulin arm and 55 additional deaths were observed on the TPC arm during this time period. For 111 of the 112 patients randomized to the eribulin arm, death was attributed to progressive disease or metastatic breast cancer; the cause of death for the remaining patient (28181005) was unknown. For 53 of the 55 patients randomized to the TPC arm, death was attributed to progressive disease. One patient death was attributed to a pulmonary embolism, and the remaining patient death was attributed to stroke.

The ADAE (adverse event) dataset was reviewed to determine if any patients experienced an adverse event that resulted in fatality between May 12, 2009 and November 30, 2009. No adverse events resulting in fatality were reported in either treatment group.

Analysis of Serious Adverse Events Occurring After Data Cut-Off Date

Ten serious adverse events experienced by 5 eribulin-treated subjects were reported for the time period of May 13, 2009 to November 30, 2009.

Table 95: SAEs Reported Following Data Cut-Off

Patient No.	PT	Toxicity Grade/Severity	Comments
11011008	Pleural Effusion	Moderate	Occurred twice; considered not related by investigator
16011005	Epilepsy	Severe	Considered not related by investigator
17061011	Osteonecrosis	Severe	Patient on concomitant bisphosphonates
24041016	Body Temperature Increased	1	
24041016	Viral Infection	1	
28121022	Back Pain	4	Lower back pain considered related by investigator; unresolved at the time of reporting
28121022	Diarrhea	4	Resolved without dose adjustment
28121022	Hypotension	3	Occurred during period of hospitalization for diarrhea; lasted 3 days; <i>most likely secondary to dehydration caused by diarrhea.</i>

Analysis of Other Adverse Events Occurring After the Data Cut-Off Date

The ADAE (adverse event) dataset included in the 120-day safety update was reviewed to determine if inclusion of the adverse events occurring from May 13, 2009 to November 30, 2009 resulted in substantial changes in the per-patient incidence of common adverse events by preferred term in eribulin-treated patients. Review of this database did not reveal changes in the per-patient incidence of adverse events that exceeded 1% for adverse events of all Grades; review of the per-patient incidence of Grade 3 or higher adverse events by preferred term derived from the 120-day Safety Update adverse event database did not reveal substantive changes to the per-patient incidence rates derived from the original submission.

Comment: No changes to the proposed label are recommended based upon review of the adverse event information included in the 120-day safety update.

8 Postmarket Experience

Because eribulin has not been approved, there is no post-marketing experience associated with this product.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

At the time of completion of this review, text for the proposed label had not been finalized. This section of the review will focus on high-level labeling recommendations. All sections of the proposed label and patient package insert were revised for clarity, brevity, and consistency. Only clinically-relevant, substantive content changes will be discussed in this section (sections pertaining to CMC or non-clinical issues are not included). Other sections of this review contain applicable discussions of labeling recommendations.

9.2.1 Indications and Usage

At the time of NDA submission, the proposed label submitted by the Applicant stated that Halaven was indicated for the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane. (b) (4)

Therefore, the indications statement for Halaven was revised to limit treatment to patients with metastatic breast cancer who have previously received an anthracycline, a taxane, and at least two chemotherapeutic regimens for the treatment of metastatic disease.

9.2.2 Dosage and Administration

The dosing information in the label proposed by the Applicant included a statement that (b) (4)

. This text was deleted due to its promotional nature.

The Warnings and Precautions section of the proposed label included a recommendation that clinicians consider reducing the starting dose for patients with ALT or AST > 3 X ULN or bilirubin > 1.5 X ULN. Based upon clinical pharmacology analysis of PK Data (see page 40 of this review for details), the following text was added to Section 2.1 of the Halaven label:

The recommended dose of Halaven in patients with mild hepatic impairment (Child's Pugh A) is 1.1 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. [see *Use in Specific Populations* (8.6)]

The recommended dose of Halaven in patients with moderate hepatic impairment (Child's Pugh B) is 0.7 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. [see *Use in Specific Populations* (8.6)]

The recommended dose of Halaven in patients with moderate renal impairment (CrCl = 30-50 mL/min) is 1.1 mg/m² administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. [see *Use in Specific Population* (8.6)]

The Dose Modification section was reformatted for clarity. In addition, in order to more closely mirror the procedures for eribulin dose adjustment used in Study 305, instructions were added for Halaven dose adjustment and delay on Day 8 for specific hematologic and nonhematologic toxicities.

In the Instructions for Preparation and Intravenous Administration section, text was added to clarify that Halaven should not be administered through an intravenous line with dextrose-containing solutions. Storage instructions were changed to limit storage of undiluted or diluted Halaven at room temperature for up to 4 hours (instead of (b) (4) for undiluted Halaven and (b) (4) hours for diluted Halaven proposed by the applicant) or refrigerated for up to 24 hours (instead of (b) (4) hours proposed by the Applicant).

9.2.3 Contraindications Section

The applicant proposed to (b) (4) This contraindication was removed because there was a lack of clinical data to support the contraindication. The incidence of adverse events consistent with hypersensitivity observed in clinical trials of eribulin was low; the integrated summary of safety indicated that 9 of a total of 827 patients (1.1%) with breast cancer treated at the target dose of eribulin exhibited allergic conditions; these conditions were limited to Grade 1 or 2 severity. Furthermore, in Study 305, the two patients who experienced hypersensitivity SAEs received subsequent cycles of eribulin (with premedication).

9.2.4 Warnings and Precautions Section

Two additional sections “Use in Women of Childbearing Potential” and “QT Prolongation” were added. In the Use in Women of Childbearing Potential section, clinicians were instructed to advise women of childbearing potential to avoid becoming pregnant and to use effective contraception during treatment with Halaven. In the QT Prolongation section, a warning of the potential for QT prolongation with eribulin use, instructions for avoidance of eribulin in patients with long QT syndrome, and ECG and electrolyte monitoring, and correction of electrolyte abnormalities in patients with specified cardiac conditions was added.

In order to more clearly characterize the primary bone marrow toxicity of eribulin, the heading (b) (4) proposed by the sponsor was changed to “neutropenia.” Additional text was added to more fully characterize the incidence and duration of neutropenia observed in Study 305 as well as the increased incidence of neutropenia and febrile neutropenia observed in patients with elevated transaminases or bilirubin levels in clinical trials of eribulin. Instructions for dose modification in patients with hepatic impairment and for delay in administration and subsequent dose reduction of Halaven in patients who experience febrile neutropenia or Grade 4 neutropenia lasting longer than 7 days was added. In lieu of proposed text recommending that (b) (4) at the initiation of Halaven treatment, a statement indicating that clinical studies did not evaluate the safety of Halaven in patients with baseline neutrophil counts below $\geq 1,500 /\text{mm}^3$ was added.

In the Neuropathy section, specific information to characterize the incidence, duration, and severity of peripheral neuropathies observed in Study 305 was added. In addition, clinicians were instructed to observe patients closely for signs of peripheral neuropathy and interrupt Halaven in patients experiencing Grade 3 or 4 neuropathy.

In the Use in Pregnancy Section, language was added regarding the expected toxicities to the fetus if Halaven is administered to a pregnant woman.

9.2.5 Adverse Reactions Section

Two paragraphs were added to provide additional information regarding the incidence of cytopenias and neuropathies. The following paragraph was also added to provide information regarding elevations in ALT and bilirubin observed in Study 305:

Liver Function Test Abnormalities: Among patients with Grade 0 or 1 ALT levels at baseline, 18% of eribulin-treated patients experienced Grade 2 or greater ALT elevation, compared to 12% of patients in the control group. One eribulin-treated patient without documented liver metastases had concomitant Grade 2 elevations in bilirubin and ALT; however, these abnormalities resolved despite rechallenge with eribulin.

The adverse event table was reordered, and adverse events that were Grade 3 and above in severity were consolidated into a single column, rather than being broken down into Grade 3 and 4 levels (as proposed by the Applicant). A few minor changes to the calculated per-patient incidence rates were made based upon review of the AE database. In addition, the Applicant was instructed to modify the per patient incidence rates of neutropenia, leukopenia, and anemia so that the per patient incidence rates of these abnormalities were based upon laboratory values, rather than reported adverse events (which would result in higher percentages being used in the Adverse Events table).

Adverse events for which there was no evidence of a causal relationship to eribulin (such as (b) (4)) were deleted.

9.2.6 Clinical Studies Section

Information characterizing the objective response rate and duration of response was added. Finally, in order for the label to reflect the most mature OS data available, Eisai was advised to use the Kaplan-Meier curve for OS based upon the updated survival data submitted on July 28, 2010 instead of the Kaplan-Meier curve derived from the primary analysis.

9.2.7 Patient Information

In conjunction with the reviewers from the Division of Risk Management and the Division of Drug, Marketing, Advertising and Communications, formatting and substantive changes were made to the Patient Package Insert (PPI) so that it complied

with 21 CFR 208.20 (MedGuide format), was an accurate reflection of the proposed label, and used language that was understandable to patients.

9.3 Advisory Committee Meeting

Because patients randomized to the eribulin arm in Study 305 experienced a clinically meaningful, statistically significant improvement in overall survival, the Office of Oncology Drug Products decided that advice from the Oncology Drugs Advisory Committee (ODAC) was not necessary in order to render a regulatory decision.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTHA B DONOGHUE
08/31/2010

STEVEN J LEMERY
08/31/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201532

Applicant: Eisai, Inc.

Stamp Date: March 30, 2010

Drug Name: Eribulin mesylate

NDA/BLA Type: NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			Quality summary, nonclinical overview, clinical overview, nonclinical written and tabulated summaries, clinical summary, literature references and synopses of individual summaries included in Module 2.
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Summarized in Section 13, page 126 of Clinical Study Report
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1) application
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Numbers: 101, 102, 105 and NCI study 5730 Study Title: E7389-A001-101:A Phase I Dose-Finding	X			Module 5.3.4.2

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			64% of enrolled patients were from North America, Western EU, Australia
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Exception: some adverse events coded mild/mod/severe instead of using CTCAE grading criteria
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			Study E7389-E044-110 in module 5.3.4.2. QT IRT consult pending
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			MedDRA Version 10.0 was used to map verbatim terms.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Module 5.3.5.1.3 Study Report Body, Section 14.3.3: Narratives of Deaths, Other SAEs, AEs leading to discontinuation, and patient deaths within 30 days of treatment
OTHER STUDIES					

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			With the exception of inconsistent grading of AEs noted above
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			249 case report forms submitted.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			All Eisai clinical studies intended to support drug approval include this statement.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Please include datasets with updated survival data that is being submitted to the EMEA by the time of the submission of the 120 day safety update.

Martha Donoghue	April 30, 2010
Reviewing Medical Officer	Date
Steven Lemery	April 30, 2010
Clinical Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTHA B DONOGHUE
04/30/2010

STEVEN J LEMERY
05/03/2010