CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201532

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review Worksheet

Addendum

Submission Date: 01-Apr-2010

NDA Number: 201,532
Product Name: eribulin mesylate
Route of Administration: intravenous infusion
Proposed Indication: locally advanced and metastatic breast cancer
Submission Type: NDA-000
Sponsor: Eisai Inc.
Reviewer: Stacy S. Shord, PharmD

Introduction
The Clinical Pharmacology and Biopharmaceutics Filing Form for NDA 201-532 (eribulin mesylate) was finalized on April 30, 2010. This is an addendum to the filing form on behalf of the clinical pharmacology review team:

For the HPLC-ESI-MS/MS method described in report no. E7389\VAL\088:
1. Provide long-term stability data of eribulin in human plasma for a minimum duration of the long-term storage of the samples collected as part of study 108, 109 and 110.
2. Provide methods to calculate inter-day precision and accuracy.

For the hepatic impairment study described in report no. E7389-E044-108:
3. Provide the data for the additional patient with moderate hepatic impairment enrolled into the study.

Recommendations: The information request will be sent to the RPM to be forwarded to the applicant.

Signatures

Stacy S Shord, Pharm.D.	Hong Zhao, Ph.D.,
Reviewer	Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DBOP: RPM – **V Jarral;** MTL –**S Lemery**; MO – **M Donoghue**
        DCP-5: DDD - **B Booth;**   DD - **A Rahman**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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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/

STACY S SHORD
05/25/2010

HONG ZHAO
05/25/2010
I concur.

APPENDIX 4.4 PRODUCT LABELING

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX 4.5 STUDY REPORTS

Study 101
Study 102
Study 103
Study 105
Study 108
Study 109
Study 110
Study 201
Study 211
Study 305

1. SUMMARY

Introduction

E7389, a synthetic analogue of halichondrin B, is a large polyether macrolide that exerts potent anti-cancer effects by inhibiting microtubule polymerization in cell-based and animal models of cancer. Pharmacokinetics (PK) of E7389 has been characterized *in vitro* and in animals following intravenous (IV) administration to support toxicology evaluation and clinical dose selection. The present Phase I clinical study was conducted in patients with advanced solid tumors to evaluate the tolerability and PK of E7389 and to determine the maximum tolerated dose (MTD) of E7389 following a one-hour IV infusion of escalating doses on Days 1, 8, and 15 every 28 days. This report summarizes the PK profiles of E7389 on Day 1 and Day 15 of Cycle 1 in patients with advanced solid tumors. The E7389 dose range evaluated was 0.25 to 1.40 mg/m^2 (in bismesylate salt equivalents).

Methods

This study was an open-label, non-randomized, multi-center, dose-finding study to determine the MTD and PK of E7389 in patients with advanced solid tumors. The treatment schedule involved administering E7389 via a one-hour infusion on Days 1, 8, 15 every 28 days. The dose of E7389 administered, based on body surface area (BSA), was expressed in mg/mL of the bismesylate salt equivalents. PK evaluation was conducted in patients on Days 1 and 15 of Cycle 1 following the first and third dose administration, respectively. Blood samples (approximately 7 mL each) were drawn from a vein in the arm opposite the IV infusion site at pre-dose and at 15, 30, 60, 65, 70, 90, and 105 minutes, and 2, 4, 8, 12, 24, 48, 72, and 96 hours following the start of IV infusion. Urine samples were collected at 0 to 24, 24 to 48, and 48 to 72 hours following the start of the IV infusion.

Plasma and urine concentrations of E7389 (in free-base equivalents) were determined using validated LC/MS/MS methods. Plasma E7389 concentration vs. time data were subjected to noncompartmental and compartmental analyses. The amount and percent of dose of E7389 recovered in urine was also calculated.

Results

A total of five single IV infusion doses of E7389 were evaluated in a total of 32 patients, i.e., a 0.25 mg/m^2 dose in 2 patients, a 0.5 mg/m^2 dose in 8 patients, a 0.7 mg/m^2 dose in 4 patients, a 1.0 mg/m^2 dose in 9 patients, and a 1.4 mg/m^2 dose in 9 patients. The patient population consists of 11 males and 21 females, with age ranging from 33 to 77 years old.

The PK parameters of E7389 determined by noncompartmental and two-compartmental analyses are summarized by dose level on Day 1 and Day 15 in the following tables.

Day 1 Pharmacokinetic Parameters of E7389 Determined by Noncompartmental Methods								
Dose[a] mg/m^2		CL L/hr/m^2	V_{ss} L/m^2	t½ hr	C_{max} µg/mL	$AUC_{0-\infty}$ hr•µg/mL	C_{max}/Dose[b] µg/mL	$AUC_{0-\infty}$/Dose[b] hr•µg/mL
0.25 (n = 2)	Mean	1.93	50.3	32.1	0.044	0.173	0.202	0.785
	Median	1.93	50.3	32.1	0.044	0.173	0.202	0.785
0.50 (n = 7)	Mean	1.90	62.3	38.0	0.079	0.338	0.179	0.766
	%CV	60	59	14	41	71	56	65
	Median	1.57	53.3	39.2	0.077	0.281	0.174	0.636
0.70 (n = 4)	Mean	1.51	43.7	35.8	0.117	0.512	0.189	0.828
	%CV	49	35	18	36	58	35	58
	Median	1.55	39.3	36.9	0.128	0.430	0.207	0.695
1.00 (n = 9)	Mean	1.92	64.8	40.5	0.144	0.653	0.163	0.739
	%CV	70	47	37	30	57	29	57
	Median	1.75	58.3	34.2	0.150	0.505	0.170	0.571
1.40 (n = 9)	Mean	1.73	59.1	37.2	0.233	0.856	0.188	0.692
	%CV	45	44	25	41	44	53	43
	Median	1.46	47.8	34.8	0.219	0.847	0.177	0.685
Overall (n = 31)	Mean	1.81	58.9	37.8	na	na	0.180	0.746
	%CV	57	48	27	na	na	37	55
	Median	1.57	53.3	36.3	na	na	0.175	0.636

Day 15 Pharmacokinetic Parameters of E7389 Determined by Noncompartmental Methods								
Dose[a] mg/m^2		CL L/hr/m^2	V_{ss} L/m^2	t½ hr	C_{max} µg/mL	$AUC_{0-\infty}$ hr•µg/mL	C_{max}/Dose[b] µg/mL	$AUC_{0-\infty}$/Dose[b] hr•µg/mL
0.25 (n = 2)	Mean	1.70	41.0	27.6	0.106	0.228	0.480	1.032
	Median	1.70	41.0	27.6	0.106	0.228	0.480	1.032
0.50 (n = 6)	Mean	1.98	67.0	41.0	0.080	0.642	0.181	1.452
	%CV	77	83	35	59	130	55	131
	Median	2.12	51.1	39.3	0.065	0.220	0.149	0.498
0.70 (n = 3)	Mean	1.89	44.3	27.4	0.112	0.526	0.181	0.850
	%CV	61	55	17	36	93	36	93
	Median	2.44	44.9	28.3	0.110	0.253	0.177	0.409
1.00 (n = 6)	Mean	2.50	65.0	32.7	0.127	0.412	0.144	0.466
	%CV	44	32	40	22	42	22	42
	Median	2.26	63.7	27.7	0.128	0.391	0.145	0.442
1.40 (n = 4)	Mean	1.88	47.3	35.6	0.247	0.913	0.200	0.738
	%CV	52	17	52	41	76	50	81
	Median	2.01	43.9	30.2	0.227	0.647	0.183	0.523
Overall (n =20)	Mean	2.05	56.5	34.5	na	na	0.202	0.930
	%CV	57	60	38	na	na	80	121
	Median	2.35	49.7	30.5	na	na	0.154	0.426

[a]: Dose is expressed as the bismesylate salt equivalent. One mg E7389 bismesylate salt is equal to (b) mg E7389 free base.
[b]: Normalized to each 1 mg/m^2 free-base dose.

Day 1 Pharmacokinetic Parameters of E7389 Determined by Two-Compartmental Model Analysis									
Dose[a] mg/m^2		CL L/hr/m^2	V_{ss} L/m^2	t½,α hr	t½,β hr	C_{max} μg/mL	$AUC_{0-\infty}$ hr•μg/mL	C_{max}/Dose[b] μg/mL	$AUC_{0\infty}$/Dose[b] hr•μg/mL
0.25 (n = 2)	Mean	1.94	44.0	0.411	26.0	0.036	0.171	0.163	0.774
	Median	1.94	44.0	0.411	26.0	0.036	0.171	0.163	0.774
0.50 (n = 7)	Mean	1.86	57.1	0.501	35.3	0.077	0.357	0.174	0.808
	%CV	61	53	38	30	43	72	43	72
	Median	1.56	49.9	0.569	32.9	0.074	0.284	0.167	0.643
0.70 (n = 4)	Mean	1.72	47.5	0.653	34.3	0.113	0.494	0.180	0.738
	%CV	64	49	49	15	33	64	56	81
	Median	1.51	39.6	0.656	34.8	0.117	0.431	0.187	0.523
1.00 (n = 9)	Mean	1.91	62.1	0.374	42.3	0.156	0.689	0.177	0.779
	%CV	72	40	31	49	34	61	57	64
	Median	1.78	56.7	0.331	33.8	0.152	0.498	0.172	0.563
1.40 (n = 9)	Mean	1.71	54.7	0.349	34.3	0.231	0.863	0.186	0.698
	%CV	44	38	22	28	32	44	54	43
	Median	1.45	46.1	0.362	31.6	0.219	0.851	0.177	0.688
Overall (n = 31)	Mean	1.81	55.8	0.434	36.3	na	na	0.178	0.763
	%CV	59	42	43	38	na	na	34	58
	Median	1.85	49.5	0.398	32.9	na	na	0.172	0.643

Day 15 Pharmacokinetic Parameters of E7389 Determined by Two-Compartmental Model									
Dose[a] mg/m^2		CL L/hr/m^2	V_{ss} L/m^2	t½,α hr	t½,β hr	C_{max} μg/mL	$AUC_{0-\infty}$ hr•μg/mL	C_{max}/Dose[b] μg/mL	$AUC_{0\infty}$/Dose[b] hr•μg/mL
0.25 (n = 2)	Mean	1.68	39.0	0.401	26.7	0.077	0.240	0.349	1.084
	Median	1.68	39.0	0.401	26.7	0.077	0.240	0.349	1.084
0.50 (n = 7)	Mean	1.99	62.3	0.506	46.5	0.081	0.762	0.183	1.725
	%CV	78	75	43	78	57	147	55	145
	Median	2.15	49.2	0.459	35.0	0.066	0.218	0.151	0.493
0.70 (n = 4)	Mean	1.86	43.2	0.499	26.3	0.112	0.529	0.180	0.855
	%CV	61	54	74	19	34	92	56	94
	Median	2.38	43.6	0.288	27.2	0.099	0.261	0.160	0.422
1.00 (n = 9)	Mean	2.49	60.2	0.296	28.3	0.126	0.409	0.143	0.463
	%CV	42	25	16	27	27	40	27	43
	Median	2.26	58.0	0.298	25.6	0.121	0.391	0.137	0.442
1.40 (n = 9)	Mean	1.87	43.9	0.413	29.4	0.229	0.889	0.186	0.719
	%CV	51	24	23	32	27	72	27	70
	Median	2.00	42.3	0.406	27.8	0.214	0.649	0.174	0.525
Overall (n = 20)	Mean	2.04	52.9	0.423	33.5	na	na	0.189	1.014
	%CV	57	55	46	64	na	na	61	144
	Median	2.32	49.2	0.332	28.2	na	na	0.155	0.432

[a]: Dose is expressed as the bismesylate salt equivalent. One mg E7389 bismesylate salt is equal to (b) mg E7389 free base.

[b]: Normalized to each 1 mg/m^2 free-base dose.

Except for three patients, all patients had measurable plasma E7389 concentrations (≥ 0.177 ng/mL) up to 96 hours following the start of IV infusion on Day 1 or Day 15. There were no major changes in E7389 PK parameters between the first and third doses administered about 2 weeks apart in the majority of patients. The disposition of E7389 follows linear kinetics over the dose range studied. This was shown by the similar or consistent dose-independent PK parameters ($t\frac{1}{2}$, CL) across dose levels, and the similar dose-normalized parameters (C_{max}/Dose and $AUC_{0\,\infty}$/Dose) between doses ranging from 0.25 to 1.40 mg/m^2. Linear kinetics and dose proportionality were also shown by Day 15 data, however, not as clear as those on Day 1 due to the smaller sample size and greater intersubject variability in E7389 plasma concentrations.

A two-compartmental model with first-order elimination best described the plasma E7389 concentration vs. time profiles on both Days 1 and 15. The noncompartmental methods and two-compartmental PK modeling resulted in consistent PK parameter estimates of E7389 on each study day.

Approximately 6.2% or 4.3% of the dose administered intravenously was eliminated as E7389 in urine over the 72 hours post-dose period across all dose levels on Day 1 or Day 15, respectively. There was incomplete urine collection in several patients and great intersubject variability in urinary recovery of E7389.

Conclusions

Following an intravenous administration of E7389 by a 60-min infusion to patients, E7389 plasma concentration-time profile exhibited a rapid distribution phase with a mean half-life of 0.43 (median: 0.40) hour, followed by a slow elimination phase with a mean half-life of 36 (median: 33) hours. The disposition of E7389 followed linear kinetics over the 0.25 to 1.40 mg/m^2 dose range studied. The mean values for systemic clearance (CL) and volume of distribution at steady state (V_{ss}) of E7389 were 1.81 (median: 1.85) L/hr/m^2 and 56 (median: 50) L/m^2, respectively, across all dose levels. The C_{max} and AUC of E7389 increased dose proportionally over the dose range studied. Urinary excretion was a minor route of E7389 elimination.

Key Words

E7389; Pharmacokinetics, Humans; Cancer; Intravenous

1.   SUMMARY

Introduction

E7389, a synthetic analogue of halichondrin B, is a large polyether macrolide that exerts potent anti-cancer effects by inhibiting microtubule polymerization in cell-based and animal models of cancer.   Pharmacokinetics (PK) of E7389 has been characterized in animals following intravenous (IV) administration to support toxicology evaluation and clinical dose selection.   Phase I clinical studies have been conducted in patients with advanced solid tumors to evaluate the tolerability and PK of E7389 and to determine the maximum tolerated dose (MTD).   The present study was conducted to further establish the MTD and determine the PK of E7389 following a one-hour IV infusion of escalating doses on Day 1 Cycle 1 of a 21-day treatment cycle in patients with advanced solid tumors that have progressed following standard therapy or for which no standard therapy exists.   This report summarizes the PK profiles of E7389 following escalating doses of 0.25 to 4.0 mg/m^2 in patients with advanced solid tumors.

Methods

This Phase I clinical study was an open-label, non-randomized, multi-center, dose-finding study in patients with advanced solid tumors.   Each dose of E7389 (bismesylate salt) was administered by constant IV infusion over one hour.   PK evaluation was conducted on Day 1 of Cycle 1 following the first dose administration.   Blood samples were drawn from a vein in the arm opposite the IV infusion site at predetermined time points up to 96 hours following the start of IV infusion on Day 1 of Cycle 1 in each patient.   Urine samples were collected up to 72 hours following the start of the infusion.

Plasma and urine concentrations of E7389 (in free-base equivalents) were determined using validated LC/MS/MS methods.   Plasma E7389 concentration vs. time data were subjected to noncomparatmental and compartmental PK analyses.   The amount and percent of the E7389 dose recovered in urine was also calculated.

Results

A total of six single IV doses of E7389 were evaluated in a total of 21 patients, i.e., a 0.25 mg/m^2 dose in 1 patient, a 0.5 mg/m^2 dose in 4 patients, a 1.0 mg/m^2 dose in 3 patients, a 2.0 mg/m^2 dose in 7 patients, a 2.8 mg/m^2 dose in 3 patients and a 4.0 mg/m^2 dose in 3 patients. The patient population consisted of 13 males and 8 females, with age ranging from 29 to 73 years old.

The PK parameters of E7389 determined by noncompartmental methods and two-compartmental model analysis are summarized by dose level in the following tables.

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Dose[a] mg/m²		CL L/hr/m²	V_{ss} L/m²	t½ hr	C_{max} μg/mL	$AUC_{0-\infty}$ hr•μg/mL	C_{max}/Dose[b] μg/mL	$AUC_{0-\infty}$/Dose[b] hr•μg/mL
		Pharmacokinetic Parameters of E7389 Determined by Noncompartmental Methods						
0.25	Mean	1.60	53.3	35.2	0.044	0.138	0.197	0.624
(n = 1)	Median	1.60	53.3	35.2	0.044	0.138	0.197	0.624
0.50	Mean	2.22	67.6	34.4	0.063	0.210	0.142	0.474
(n = 4)	%CV	26	37	20	29	26	29	26
	Median	2.18	62.1	31.9	0.062	0.204	0.140	0.462
1.0	Mean	2.42	86.7	45.9	0.127	0.486	0.144	0.550
(n = 3)	%CV	57	13	48	31	68	31	68
	Median	2.45	84.0	42.7	0.127	0.362	0.144	0.409
2.0	Mean	1.16	47.8	48.8	0.369	1.842	0.209	1.042
(n = 7)	%CV	47	21	45	10	46	10	46
	Median	0.97	46.6	35.8	0.382	1.816	0.216	1.028
2.8	Mean	2.12	87.4	42.3	0.340	1.412	0.138	0.571
(n = 3)	%CV	59	56	16	39	44	39	44
	Median	1.44	73.0	42.5	0.316	1.720	0.128	0.695
4.0	Mean	1.70	114.2	66.0	0.528	2.334	0.149	0.660
(n = 3)	%CV	44	14	33	34	39	34	39
	Median	1.47	113.7	69.4	0.540	2.411	0.153	0.682
Overall	Mean	1.78	72.5	46.5	na	na	0.168	0.722
(n = 21)	%CV	50	43	40	na	na	28	55
	Median	1.59	63.3	42.5	na	na	0.183	0.629

[a] Dose is expressed as the bismesylate salt equivalent. One mg E7389 bismesylate salt is equal to (b) (4) E7389 free base. [b] Normalized to each 1 mg/m² free-base dose. na: not applicable

Dose[a] mg/m²		CL L/hr/m²	V_{ss} L/m²	t½,α hr	t½,β hr	C_{max} μg/mL	$AUC_{0-\infty}$ hr•μg/mL	C_{max}/Dose[b] μg/mL	$AUC_{0-\infty}$/Dose[b] hr•μg/mL
		Pharmacokinetic Parameters of E7389 Determined by Two-Compartmental Model Analysis							
0.25	Mean	1.59	50.1	0.374	31.8	0.039	0.139	0.177	0.628
(n = 1)	Median	1.59	50.1	0.374	31.8	0.039	0.139	0.177	0.628
0.50	Mean	2.23	64.3	0.528	31.1	0.059	0.209	0.133	0.472
(n = 4)	%CV	26	32	32	16	27	26	27	26
	Median	2.17	62.7	0.531	31.0	0.058	0.206	0.132	0.465
1.0	Mean	2.37	83.6	0.395	44.0	0.116	0.490	0.131	0.555
(n = 3)	%CV	58	7	33	49	28	66	28	66
	Median	2.30	83.5	0.332	39.7	0.115	0.385	0.131	0.435
2.0	Mean	1.11	40.9	0.535	41.6	0.357	1.845	0.202	1.044
(n = 7)	%CV	42	21	41	45	7	41	7	41
	Median	0.96	40.8	0.453	35.0	0.364	1.832	0.206	1.037
2.8	Mean	2.15	79.2	0.377	37.6	0.360	1.400	0.145	0.566
(n = 3)	%CV	60	54	18	18	33	44	33	44
	Median	1.44	67.8	0.402	37.8	0.382	1.723	0.154	0.696
4.0	Mean	1.70	92.5	0.269	52.6	0.537	2.215	0.152	0.627
(n = 3)	%CV	31	19	5	17	23	29	23	29
	Median	1.56	92.2	0.264	48.2	0.508	2.262	0.144	0.640
Overall	Mean	1.76	64.7	0.446	40.5	na	na	0.162	0.717
(n = 21)	%CV	50	41	39	36	na	na	25	52
	Median	1.56	52.2	0.392	37.2	na	na	0.175	0.640

[a] Dose is expressed as the bismesylate salt equivalent. One mg E7389 bismesylate salt is equal to (b) E7389 free base. [b] Normalized to each 1 mg/m² free-base dose. na: not applicable

All patients had measurable plasma E7389 concentrations (> 0.177 ng/mL) up to 96 hours following the start of IV infusion. The disposition of E7389 follows linear kinetics over the dose range studied. This was shown by the similar or consistent dose-independent PK parameters ($t\frac{1}{2}$, CL) across dose levels, and the similar dose-normalized parameters (C_{max}/Dose and $AUC_{0\ \infty}$/Dose) between 0.25 to 4.0 mg/m^2.

A two-compartmental model with first-order elimination best described the plasma E7389 concentration vs. time profiles. The noncompartmental methods and two-compartmental modeling resulted in consistent PK parameter estimates of E7389.

Approximately 8.4% of the dose administered was eliminated in urine over the 72 hours post-dose period across all dose levels. There was great intersubject variability in urinary recovery of E7389.

Conclusions

Following a 60-min IV infusion of E7389 in cancer patients, E7389 plasma concentration-time profile exhibited a rapid distribution phase with a mean half-life of 0.45 (median: 0.39) hour, followed by a slow elimination phase with a mean half-life of 41 (median: 37) hours, across all dose levels. The disposition of E7389 follows linear kinetics over the 0.25 to 4.0 mg/m^2 dose range studied. The mean systemic clearance (CL) and volume of distribution at steady state (V_{ss}) of E7389 were 1.76 (median: 1.56) L/hr/m^2 and 65 (median: 52) L/m^2, respectively, across all dose levels. The C_{max} and AUC values of E7389 increased nearly dose proportionally over the dose range studied. Urinary excretion was a minor route of E7389 elimination.

Key Words

E7389; Pharmacokinetics; Humans; Cancer; Intravenous

2   SYNOPSIS

Name of Sponsor Company: Eisai	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product:	Volume:	
Name of Active Ingredient: Eribulin mesylate	Page:	

Title of Study: An Open-Label, Non-Randomized, Single-Center Study to Determine the Metabolism and Elimination of Carbon-14 labeled Eribulin Acetate (^{14}C-Eribulin) in Patients with Advanced Solid Tumors

Study Number: E7389-E044-103

Investigator: Professor Jan Schellens, MD, PhD

Study center: The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Study Period	From: 09 March 2009 (first patient in) To: 02 June 2009 (end of study phase)	**Clinical Phase:** Phase 1

Objectives:
Primary: To determine the excretion balance and to elucidate the metabolic pathway of eribulin in vivo after a single dose of carbon-14 radio-labeled eribulin (^{14}C-eribulin), in patients with advanced solid tumors.
Secondary: To assess the safety and tolerability of eribulin, and assess response in patients with advanced solid tumors who are unsuitable for or have failed existing therapies when given multiple doses of non-radio-labeled eribulin mesylate.

Methodology: This was an open-label, non-randomized, single-center study to determine the metabolism and elimination of ^{14}C-eribulin, the carbon-14 labeled acetic acid salt form of eribulin, in patients with advanced solid tumors that had progressed following standard therapy or for which no standard therapy existed. Patients were to receive a 2 mg flat dose of ^{14}C-eribulin acetate on Day 1 of Cycle 1 only. Thereafter, the dose regimen of 1.4 mg/m^2 of non-radio-labeled eribulin mesylate was to be given on Day 8 of Cycle 1 and on Days 1 and 8 of each subsequent 21-day cycle. This synopsis provides data for the Study phase. Data from subsequent cycles will be reported separately.

Number of Patients:
- Number of patients planned: Up to a maximum of 10 patients was planned. A minimum of 6 evaluable patients was required with a minimum of 2 women and 2 men.
- Number of patients enrolled: 6
- Number of patients analyzed for safety: 6
- Number of patients analyzed for pharmacokinetics: 6

Diagnosis and Criteria for Inclusion: Patients of at least 18 years of age who had a histologically or cytologically confirmed advanced solid tumor that had progressed following standard therapy or for which no standard therapy existed.

Test Product: Non-radio-labeled drug product: eribulin mesylate Eisai standard 1.0 mg (as mesylate salt) in 0.1 mL ethanol plus 1.9 mL water for injection. Radio-labeled drug: ^{14}C-eribulin acetate 40 to 45 μCi/mg as ethanol solution (target concentration 10 mg/mL).
Dose: Single 2 mg flat dose of ^{14}C-eribulin acetate (approximately 80 to 90 μCi) on Cycle 1 Day 1, and non-radio-labeled eribulin mesylate at a dose of 1.4 mg/m^2 on Cycle 1 Day 8. Thereafter, non-radio-labeled eribulin mesylate at a dose of 1.4 mg/m^2 on Days 1 and 8 of each 21-day cycle.
Mode of Administration: ^{14}C-eribulin acetate (Cycle 1 Day 1 only) and non-radio-labeled eribulin mesylate were to be administered as an intravenous (IV) infusion over 2 to 5 minutes.
Lot Number: non-radio-labeled eribulin mesylate N0600720, ^{14}C-eribulin acetate CFQ40373 (Batch 1)
Expiry Date: non-radio-labeled drug: 24 October 2010; radio-labelled drug did not have expiry date, but a retest date of 8th May 2009, due to ongoing stability testing.

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Reference Product, Dose and Mode of Administration, Lot Number, Expiry Date:
Not applicable

Duration of Treatment: Patients who demonstrated clinical benefit could continue to receive eribulin mesylate at a dose of 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle until one of the following occurred: progressive disease; loss of clinical benefit due to toxicity; withdrawal of consent; presence of other medicinal conditions that prohibited continuation with therapy; pregnancy; failure of the patient to comply with study procedures which compromised safety; delay of more than 14 days in starting the next cycle due to toxicities; presence of new medical information that warranted the termination of the study; termination of the study by the Sponsor for safety reasons; or the Investigator concluded that further therapy was not in the best interest of the patient.

Criteria for Evaluation:
Pharmacokinetics: Plasma, urine, and fecal concentrations of ^{14}C-eribulin related material were assessed after the single dose of ^{14}C-eribulin acetate using scintillation counting and liquid chromatography tandem mass spectroscopy. The following pharmacokinetic (PK) parameters of ^{14}C-eribulin and parent eribulin (free base) in plasma were to be determined: maximum observed plasma concentration (C_{max}); time of maximum observed plasma concentration (t_{max}); the apparent terminal disposition rate constant (λz); terminal half life ($t_{1/2z}$); area under the plasma concentration-time curve (AUC_{0-t}); area under the plasma concentration-time curve from zero to infinity (AUC_{0-inf}); percentage of area under the curve extrapolated to infinity (%AUC_{extra}); clearance (CL) for parent compound only; apparent volume of distribution in the terminal phase (V_z) for parent compound only; apparent volume of distribution at steady state (V_{ss}) for parent compound only; and renal clearance (CL_R) for parent compound only. The percent of dose of ^{14}C-eribulin and parent eribulin excreted in urine and feces ($Ae_{urine\%}$ and $Ae_{feces\%}$) from time of dosing to the last quantifiable measurement were to be determined.

Genotyping: Blood samples taken at the Screening visit were retained for pharmacogenomic analysis and enzyme polymorphism testing.

Efficacy: Tumor assessments were performed at Baseline, and thereafter between Day 15 and Day 21 of the treatment cycle at appropriate clinical intervals according to the study site's usual practice, or sooner if there was evidence of disease progression. A best response according to Response Evaluation Criteria in Solid Tumors (RECIST) was documented by the Investigator for each patient. These data will be reported separately.

Safety: Adverse events (AEs) and concomitant medications were assessed throughout the study. A full physical examination was performed at Screening, on Day 1 of the first 2 cycles, and at Study Termination. On all other visit days a symptom-directed physical exam was performed. Vital signs were recorded pre-dose on Days 1 and 8 for all cycles, post-dose on Day 1 of Cycle 1 only, and daily for Days 2 to 7 of Cycle 1 only. Thereafter, measurement was to be symptom-directed at every visit (pre-dose). Laboratory assessments were performed at Screening; on Days 1, 8 and 15 of Cycle 1; on Days 1 and 8 of subsequent cycles; and at Study Termination. Urinalysis was performed at Screening, Day 1 and Day 8 of Cycle 1, on Day 1 of each subsequent cycle, and at Study Termination. A 12-lead electrocardiogram (ECG) was taken at Screening, on Day 8 of Cycle 2, and at the Study Termination visit.

Statistical Methods:
Pharmacokinetics: All patients who received a full dose of study treatment and had evaluable post-^{14}C-eribulin dose plasma concentration data were included in the PK population. PK analysis of plasma eribulin (free base) concentrations was conducted using non-compartmental analysis. All concentration data,

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PK parameters, urinary and fecal recovery of eribulin, and total radioactivity, were tabulated and listed as appropriate. Descriptive statistics included: N, arithmetic and geometric mean, median, standard deviation, coefficient of variability, maximum and minimum. Individual and mean plasma concentration versus time profile plots were produced. Plasma concentration and dose recovery of ^{14}C-eribulin and eribulin were plotted.

Genotyping: The relationship between CYP3A (both CYP3A4 and CYP3A5) and CYP2C9 predicted phenotypes and eribulin exposure was investigated, but no formal statistical analysis was planned.

Efficacy: These data will be reported separately.

Safety: All patients who were enrolled and received at least a partial dose of study treatment were included in the safety population. The incidence of AEs, out of range laboratory safety test values, abnormal 12-lead ECGs, and physical examination findings were summarized along with changes from Baseline in laboratory safety test variables and vital signs measurements. Concomitant medications were also summarized.

RESULTS:

Pharmacokinetics: Exposure to eribulin (mean dose-normalized $AUC_{(0-t)}$ 301 ng.hr/mL/mg) was comparable to total radioactivity exposure (mean dose-normalized $AUC_{(0-t)}$ 269 ng eq.hr/mL/mg) in plasma. The mean ratio of time-matched eribulin concentrations to total radioactivity in both plasma and blood was approximately unity. Thus, the unchanged parent compound constitutes almost the entire drug-derived radioactivity in plasma, indicating that low concentrations of circulating metabolites are being formed.

Mean eribulin pharmacokinetic parameters for total radioactivity and eribulin are summarized in Table 1S.

Table 1S   Mean (SD) Pharmacokinetic Parameters for Total Radioactivity and Eribulin in Plasma: Pharmacokinetic Population

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

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

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The elimination half-life of eribulin (45.6 hr) was comparable to the elimination half-life of the total radioactivity (42.3 hr). CL_R (0.301 L/hr) represented a minor component of total CL for eribulin (3.93 L/hr).

Total recovery of the radioactive dose in urine and feces for samples collected up to 312 hr post-dose was 90.4% (range 76.5 to 111%; see Figure 1S).

Figure 1S **Mean (SD) Total (Urine and Feces) Cumulative Dose Recovery (%) of Total Radioactivity and Eribulin Following Administration of ^{14}C-Eribulin Acetate to Patients with Solid Tumors: Pharmacokinetic Population**
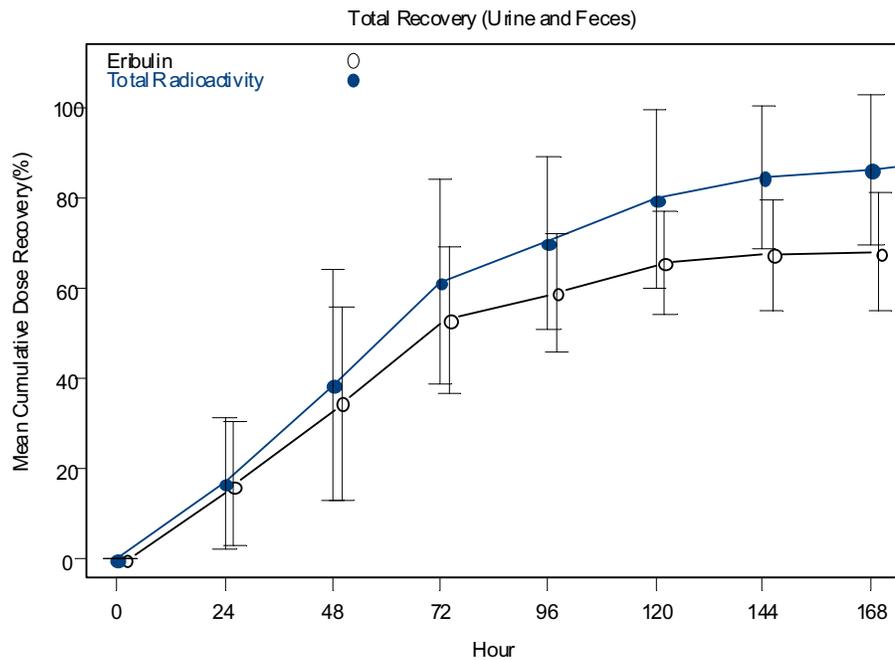
Total recovery of the radioactive dose in urine and feces for samples collected up to 312 hr post-dose was 90.4% (range 76.5 to 111%). Mean total recovery of eribulin in urine and feces for a similar collection period up to 312 hr post-dose was 68.6% (range 48.4 to 87.4%).

The mean cumulative percent dose recovery of total radioactivity in urine and feces was 90.4% (range 76.5 to 111%).

Eribulin-derived radioactivity was excreted primarily in the feces. The total radioactivity excreted in the feces accounted for 81.5% of the dose. Most of the total radioactivity (77.5%) was excreted in the feces within 168 hr post-dose.

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Cumulative recovery of total radioactivity in the feces was 81.5%. Unchanged eribulin accounted for most of the total radioactivity (87.6%) excreted up to 72 hr post dose. The relative contribution of eribulin versus the total radioactivity slightly decreased at later time intervals. For example, at 312 hr post dose, only 76.0% of the radioactivity recovered in feces was parent drug.

Cumulative dose recovery of the total radioactivity in the urine was 8.9% (range 5.42% to 16.4%). Eribulin represented most (~91%) of the total radioactivity excreted in the urine, indicating that almost all of the drug-derived radioactivity recovered in the urine was unchanged parent drug. Total radioactivity excretion in the urine was almost complete (7.5% of the dose) by 72 hr post-dose, with the remaining urinary fractions collected for up to 168 hr post-dose contributing <0.5% of the dose each. These data indicate that CL_R is not a significant route of elimination for eribulin.

Genotyping: The majority of patients (5/6) were carriers of the CYP2C9 *1/*1 and CYP3A4 *1/*1 genotypes, and were classified as CYP2C9 and CYP3A4 extensive metabolizers; 1 patient was classified as a CYP2C9 and CYP3A4 intermediate metabolizer. Most patients (5/6) were CYP3A5 poor metabolizers, as expected in this cohort since the most common form of CYP3A5 in Caucasians is the *3/*3 form, which creates a non-active enzyme. Thus, there was very little sequence variability in any CYP enzyme in this study population.

Efficacy: These data will be reported separately.

Safety: During the Study phase, a total of 4/6 patients experienced at least 1 TEAE; and 4/6 patients experienced at least 1 TEAE reported to be treatment-related. The most common TEAE reported as treatment-related was fatigue (3/6 patients). The majority of AEs reported during the Study phase were CTC Grade 1 or 2; Grade 3 TEAEs were reported for 1 patient. There were no deaths or SAEs, and no patients were withdrawn from study treatment due to a TEAE. There were no dose reductions or delays due to TEAEs.
No significant abnormalities in laboratory parameters were reported. There were no obvious changes in vital signs reported.

CONCLUSIONS:
- Metabolism represented a minor component for eribulin elimination.
- Eribulin-related material was primarily excreted in the feces.
- CL_R represented a minor component of eribulin elimination.
- No major metabolites of eribulin were detected in plasma. Each metabolite represented ≤0.6% of eribulin in plasma.
- Eribulin mesylate was generally safe and well tolerated.

Date of the Report: 22 February 2010

2. SYNOPSIS

Name of Sponsor/Company: Eisai Co., Ltd	Summary Tables of the Study	*(For National Authority Use Only)*
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Study title: Phase I Clinical Study of E7389

Investigator(s): Toru Mukohara (See Appendix 16.1.4.a)

Study center(s): National Cancer Center Hospital East (See Appendix 16.1.4.a)

Publication (reference): None

Studied period: approximately 1 year and 7 months May 29, 2006 (date of informed consent acquisition of first subject) January 8, 2008 (date of follow-up assessment of last subject)	**Phase of development:** Phase I

Objectives:

Primary objective: To determine the dose limiting toxicity (DLT) of intravenous injection of E7389 and estimate the maximum tolerated dose (MTD) in patients with solid tumors.

Secondary objectives:
      (1)To evaluate the safety and tolerability.
      (2)To evaluate the pharmacokinetics.
      (3)To estimate the recommended dose (RD) in Phase II clinical studies.
      (4)To observe the antitumor effect in evaluable subjects.

Methodology: A stepwise ascending, single-center, non-randomized, open-label study

Number of patients (planned and analyzed):

Planned: approximately 24 patients (3 to 6 patients per dose level)

Analyzed: 15 patients (3 patients in the 0.7 mg/m^2 group, 3 patients in the 1.0 mg/m^2 group, 6 patients in the 1.4 mg/m^2 group and 3 patients in the 2.0 mg/m^2 group)

Diagnosis and criteria for inclusion:

Patients with solid tumors meeting all of the inclusion criteria and none of the exclusion criteria listed below were included in the study.

Inclusion Criteria:
  (1)Patients with histologically or cytologically confirmed solid tumors.
  (2)Patients who have tumors for which no standard therapy exists or become refractory to standard therapy and have no other treatment options.
  (3)Patients aged ≥ 20 - < 75 when giving informed consent.
  (4)Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
  (5)Patients who can stay in hospital for 2 weeks from the start of study drug treatment (till the last blood collection for plasma drug determination).
  (6)Patients having adequate function of major organs (bone marrow, liver, kidney and lungs).
    1)Neutrophil count ≥ 1,500/mm^3
    2)Platelet count ≥ 100,000/mm^3
    3)Hemoglobin ≥ 9.0 g/dL
    4)Aspartate aminotransferase (AST) ≤ 2.5 times the upper limit of the normal range used by the study center; however, ≤ 5.0 times the upper limit of the normal range in patients with hepatic metastasis
    5)Alanine aminotransferase (ALT) ≤ 2.5 times the upper limit of the normal range used by the study center; however, ≤ 5.0 times the upper limit of the normal range in patients with hepatic metastasis

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   6)Total bilirubin ≤ 1.5 times the upper limit of the normal range used by the study center

   7)Serum creatinine ≤ 1.5 times the upper limit of the normal range used by the study center

   8)Percutaneous arterial oxygen saturation (SpO_2) ≥ 90%

(7)Patients who have no carryover of effect from prior therapy or adverse drug reactions (excluding alopecia etc.) that may affect the safety evaluation of the study drug. The drug-free periods required from the completion of prior therapy to the start of study drug therapy are as follows:

   1)Four weeks or longer: chemotherapy (excluding oral 5-FU and molecular target drugs), surgical therapy, other study drugs

   2)Six weeks or longer: nitrosourea agents, mitomycin C

   3)Two weeks or longer: radiotherapy, endocrinotherpy, immunotherapy (including Picibanil), oral 5-FU, molecular target drugs, blood transfusion, blood products, G-CSF and other hematopoietic factors

(8)Patients who give written informed consent.

(9)Patients with an expected survival of ≥ 3 months from the start of study drug therapy.

Exclusion Criteria:

(1)Patients with systemic infection with a fever (≥ 38.0°C).

(2)Patients with pleural effusion, ascites or pericardial fluid requiring drainage.

(3)Patients with brain metastasis presenting clinical symptoms.

(4)Patients with serious complications:

   1)Patients with ischemic heart disease not controllable by treatment or heart disease such as arrhythmia (excluding left ventricular hypertrophy and mild left ventricular volume overload associated with hypertension, and mild right bundle-block).

   2)Patients with myocardial infarction within 6 months prior to study entry.

   3)Patients with a complication of hepatic cirrhosis.

   4)Patients with interstitial pneumonia or pulmonary fibrosis.

   5)Patients with a bleeding tendency.

(5)Pregnant women or nursing mothers (Women of childbearing potential must all be confirmed to be not pregnant before registration. Post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Female subjects must use adequate contraceptive devices. Premenopausal women who have been amenorrheic for ≥ 12 months may be considered postmenopausal).

(6)Fertile men who are not willing to use contraception.

(7)Patients who have tested positive for human immunodeficiency virus (HIV), hepatitis C virus (HCV) antibody, or hepatitis B virus surface (HBs) antigen.

(8)Patients who need continuous systemic steroid therapy during the study period.

(9)Patients who need continuous use of drugs that inhibit the drug-metabolizing enzyme CYP3A4 or drugs or foods that induce CYP3A4 during the study period.

(10)Patients who have received extensive radiotherapy (30% or more of bone marrow).

(11)Patients who refused to receive the supportive therapy of blood transfusion because of myelosuppression etc.

(12)Patients who are participating in other clinical studies.

(13)Patients who are judged inappropriate for this study by the investigator or subinvestigator.

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Test product, dose and mode of administration, batch number:

Investigational product and comparator:

   Investigational product: E7389

   Comparator: not applicable

Dose and mode of administration:

Dose:

The first dose level was set at 0.7 mg/m^2, and the safety at each dose level was evaluated in 3 or 6 patients.   Whether or not patients could receive the next dose level was determined based on the DLT observed during the first cycle.

Dose level	Dose
Level 1	0.7 mg/m^2
Level 2	1.0 mg/m^2
Level 3	1.4 mg/m^2
Level 4	2.0 mg/m^2

Mode of administration:

A cycle consisted of 3 weeks.   Each dose level of E7389 was administered once a week for two consecutive weeks (Days 1 and 8) and the third week was employed as the washout period. Administration was continued unless the study discontinuation criteria were met.

E7389 was administered intravenously over 2 to 10 minutes.   E7389 injection solution was prepared as follows: 2 mL of E7389 was drawn from a vial of E7389 (2 mL) and diluted by adding 8 mL of saline to obtain the diluted solution of 10 mL.   The appropriate volume of the diluted solution corresponding to the relevant dose level was withdrawn by syringe and administered to each patient.   The volume of saline to be added can be increased up to the total volume of 50 mL, as required.

Batch number (Lot No.):

  E7389 (2 mL vial): P57008ZZA

Duration of treatment:

A cycle consisted of 3 weeks.   E7389 was administered intravenously over 2 to 10 minutes once a week for two consecutive weeks (Days 1 and 8) and the third week was employed as the washout period.

Administration was continued unless the study discontinuation criteria were met.

Criteria for evaluation:

Primary endpoints: DLT and MTD

Secondary endpoints:

  · Adverse events (AEs), adverse drug reactions (ADRs), laboratory test results, electrocardiogram, general findings (vital signs and performance status [PS]), and body weight

  · Pharmacokinetics

  · Antitumor activity

Background of subjects:

Diagnosis at onset, history of previous treatments, primary lesion, metastatic lesion, complications, sex, age, height, body weight and body surface area

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Efficacy:
  (1) Tumor evaluation (target lesions, non-target lesions and presence/absence of occurrence of new lesion) and best overall response
    In patients evaluable for efficacy, the tumor response was evaluated by observing tumor lesions according to the RECIST (Response Evaluation Criteria in Solid Tumors).
  (2) Tumor marker
    Appropriate tumor markers were specified and measured.

Pharmacokinetics:
  (1) Plasma concentration of E7389
  (2) Urinary concentration of E7389

Safety:
DLT, AEs, symptoms and signs, general findings (blood pressure, pulse rate, body temperature, and PS), body weight, 12-lead electrocardiogram (ECG), chest X-ray, pregnancy test, and laboratory tests described below
  · Hematology
    White blood cell count, neutrophil count, lymphocyte count, red blood cell count, hemoglobin, platelet count
  · Blood biochemistry
    Total protein, total cholesterol, glucose, albumin, total bilirubin, BUN, serum electrolytes (Cl, Na, K, Ca, P), Al-P, AST, ALT, γ-GTP, LDH, CPK, serum creatinine, and CRP
  · Urinalysis
    Protein (qualitative), glucose (qualitative), and occult blood
  · Others
    SpO_2

The severities of AEs observed during the study were judged based on the "CTCAEv3.0 in Japanese." The severity of an event on which no information about specific symptoms or laboratory values was available in the "CTCAEv3.0 in Japanese" was to be judged by the investigator or subinvestigator according to the following criteria:
  · Grade 0:   Normal
    no adverse event or within normal limits
  · Grade 1:   Mild adverse event
    minor, no specific medical intervention, asymptomatic laboratory findings only, radiographic findings only, marginal clinical relevance
  · Grade 2:   Moderate adverse event
    minimal intervention, local intervention, noninvasive intervention
  · Grade 3:   Severe adverse event
    significant symptoms requiring hospitalization or invasive intervention, transfusion, elective interventional radiological procedure, therapeutic endoscopy or operation
  · Grade 4:   Life-threatening or disabling adverse event
    complicated by acute life-threatening metabolic or cardiovascular complications; intensive care or emergent interventional radiological procedure, therapeutic endoscopy or operation
  · Grade 5:   Death related to adverse event

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Others:
Status of drug administration, concomitant therapies (concomitant medications and other concomitant therapies), and survival outcome

Statistical Methods:

Efficacy analysis:
For each dose level and the whole population, the numbers of patients in whom the best overall response was evaluated as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE) were calculated from evaluable patients. The number of patients with response (number of patients evaluated as CR or PR), the response rate and 95% confidence interval were calculated for each dose level and the whole population. In addition, a transition curve expressing the decrease ratio in the sum of the longest diameter of target lesions and the change in tumor markers was prepared for each patient.

Pharmacokinetic analysis:
Pharmacokinetic parameters were calculated from plasma concentration data of E7389 using model independent analysis and compartment model analysis. For dose level 1 to 4, the dose proportionality was examined using C_{max} and AUC_{0-t} values obtained by model independent analysis. In addition, the plasma E7389 concentration-time profile and the cumulative urinary excretion of E7389 were investigated by plotting the data.

<Pharmacokinetic parameters>
Maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC), terminal elimination rate constant (λz), terminal elimination half-life ($t_{1/2}$), distribution volume at the terminal elimination phase (Vz), mean residence time (MRT), total clearance (CL) and renal clearance (CL_R)

Safety analysis:
Regarding DLT (a primary endpoint) occurred during Cycle 1, the number of events, number of patients with DLTs, incidence and 95% confidence interval were calculated for each dose level and the whole population. The data were summarized separately depending on types of DLTs.

Regarding AEs and ADRs occurred during Cycle 1 and whole study period, the number of events, number of patients with them, incidence and its 95% confidence interval were calculated for each dose level and the whole population. The number of events, number of patients with them and incidence were summarized by causal relationship and severity (according to the grades specified in "CTCAE v3.0 in Japanese"), and the same summarization was also performed, separated by symptoms/findings (system organ classes [SOC] and preferred terms [PT] coded according to MedDRA/J). In addition, AEs and ADRs were summarized by the onset time and resolution time, and further detailed summarization was performed for white blood cell count decreased and neutrophil count decreased.

Regarding body weight, general findings and laboratory tests, the transition curves and shift tables for each parameter were prepared for each dose level and the whole population. The summary statistics of measurements and changes at each evaluation time point were also calculated. For parameters specified in "CTCAE v3.0 in Japanese," the change in grade between before and after drug administration was summarized. The relationships between the plasma pharmacokinetic parameters

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(C_{max} and AUC_{0-t}) of E7389 and the nadir of hematological variables or the rate of decrease from before treatment were expressed as scatter plots to be evaluated.

SUMMARY – CONCLUSIONS:

EFFICACY RESULTS:

In this study, the 15 enrolled patients were all included in the efficacy analysis set. Of these, 14 patients could be evaluated for tumor response according to RECIST and 3 patients were found to have response (all PR). Three patients with response were all in the 1.4 mg/m^2 group and consisted of one with head and neck cancer (registration number: 301) and two with non-small cell lung cancer (registration numbers: 303 and 305). In this study, 2 patients with breast cancer, which is the target disease of an ongoing Japanese phase II study, were enrolled in the 2.0 mg/m^2 group (registration numbers: 401 and 402). Although the best overall response was evaluated as SD in both these patients, the maximum decrease ratio in the sum of the longest diameter of target lesions was 10.9% (Day 75 after starting study treatment) and 22.8% (Day 79 after starting study treatment) in the respective patients. From the above results, it was suggested that E7389 would have the clinical efficacy on solid tumors.

PHARMACOKINETIC RESULTS:

Fifteen patients (3 patients each in the 0.7, 1.0 and 2.0 mg/m^2 groups, 6 patients in the 1.4 mg/m^2 group) were included in the pharmacokinetic analysis set. In the pharmacokinetic analyses, E7389 concentrations and pharmacokinetic parameters were expressed as the E7389 free base, while the doses were expressed as the mesylate salt equivalent. One mg E7389 mesylate salt is equivalent to (b) (4) mg E7389 free base.

After E7389 was administered intravenously over 2 to 10 minutes at doses of 0.7, 1.0, 1.4 and 2.0 mg/m^2, E7389 was eliminated triphasically. The mean $t_{1/2}$ values calculated from the plasma concentration-time profiles on Day 1 of Cycle 1 ranged between 36.4 and 59.9 hours. The mean CL values ranged between 1.32 and 2.37 L/hr/m^2, and the mean V_z values between 105.6 and 143.0 L/m^2. Pharmacokinetic parameters on Day 8 were comparable with those on Day 1.

Urine was collected up to 72 hours after E7389 was administered intravenously over 2 to 10 minutes at doses of 0.7 to 2.0 mg/m^2 to investigate the urinary excretion of E7389. On average, 5.01 to 12.88% of the dose of E7389 were excreted in urine until 72 hours after drug administration, with CL_R ranging between 220.5 to 454.4 mL/hr.

The dose proportionality was examined visually on C_{max} and AUC_{0-t} values obtained by model independent analysis, and it was found that the increase in C_{max} was proportional to the dose but that in AUC_{0-t} was more than proportional to dose. In a formula $Y=\alpha X^{\beta}$, in which the dose was assigned to X and the C_{max} or AUC_{0-t} value to Y, the point estimate of β and its 95% confidence interval were calculated. The point estimate of β was 0.868 for C_{max}, being close to 1, but that for AUC_{0-t} was 1.527, being greater than 1. The 95% confidence intervals of β were 0.610 to 1.125 for C_{max} and 1.162 to 1.891 for AUC_{0-t}, neither of them meeting the criterion for dose proportionality.

SAFETY RESULTS:

In this study, the 15 enrolled patients were all included in the safety analysis set. DLTs were observed in 2 out of 6 patients in the 1.4 mg/m^2 group and 3 out of 3 in the 2.0 mg/m^2 group. The details of

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DLTs occurred in these 5 patients were as follows (multiple count): "grade 4 neutropenia (less than 500/mm^3) lasting for 5 days or longer" in 2 patients; "grade 3 or higher febrile neutropenia (38.5°C or higher)" in 2 patients; and, "skipped administration due to grade 3 or higher neutropenia (less than 1,000/mm^3) at the initiation of drug administration on Day 8 in the cycle" in 4 patients. Based on the above results, it was estimated that the MTD of E7389 in Japanese patients with solid tumors would be 2.0 mg/m^2 and the RD for phase II studies would be 1.4 mg/m^2.

In 15 patients included in the safety analysis set, the incidence of AEs and that of ADRs were both 100.0%. The frequently reported AEs in the whole study period were as follows: lymphocyte count decreased (86.7%, 13/15); white blood cell count decreased (86.7%, 13/15); neutrophil count decreased (80.0%, 12/15); and, blood glucose increased (80.0%, 12/15). Although the percentage of events of grade 3 or higher was as high as 66.7% (10/15) for white blood cell count decreased and neutrophil count decreased, it was only 20.0% (3/15) for lymphocyte count decreased and the severity of all events of blood glucose increased was grade 2 or lower (mild to moderate). The frequently reported ADRs were as follows: lymphocyte count decreased (86.7%, 13/15); white blood cell count decreased (86.7%, 13/15); neutrophil count decreased (80.0%, 12/15); and, blood glucose increased (73.3%, 11/15).

In this study, as serious adverse events (SAEs) occurred during a period from the first administration of E7389 to the final observation, 2 events were reported in separate patients (registration number: 305 in the 1.4 mg/m^2 group; registration number: 402 in the 2.0 mg/m^2), both being hospitalization due to febrile neutropenia. As SAEs occurred during a period from the final observation to 30 days after the last administration of E7389, 3 events were reported in 2 patients (registration number: 103 in the 0.7 mg/m^2 group [hospitalization due to vomiting]; registration number: 304 in the 1.4 mg/m^2 group [hospitalization due to nausea and abdominal pain]). In this study, no death was reported until 30 days after the last administration of E7389. In addition, after 30 days elapsed from the last administration of E7389, one event of serious ADR unexpected from the Investigator's Brochure (myelodysplastic syndrome) occurred in one patient (registration number: 201 in the 1.0 mg/m^2 group).

As significant AEs observed in this study, those determined as DLT were neutrophil count decreased and febrile neutropenia. Throughout the whole study period, AEs of grade 3 or higher were observed in 2 out of 3 patients in the 0.7 mg/m^2 group, 2 out of 3 in the 1.0 mg/m^2 group, 6 out of 6 in the 1.4 mg/m^2 group, and 3 out of 3 in the 2.0 mg/m^2 group. The most frequently reported AEs of grade 3 or higher were neutrophil count decreased and white blood cell count decreased (both 66.7%, 10/15). In addition, the number of patients who discontinued the study treatment due to AEs was one each in the 1.0 mg/m^2 and 2.0 mg/m^2 groups, and the AE was platelet count decreased in both patients.

Among laboratory parameters, those in which deterioration of three grades or greater compared to values before the study treatment was observed during the whole study period were neutrophil count and white blood cell count. In the 1.4 mg/m^2 and 2.0 mg/m^2 groups, neutrophil count decreased of grade 3 or higher, classified as ADR, was observed in all patients. In these patients, the median (minimum to maximum) of the period starting from the Day 1 of the cycle in which there was an occurrence of the ADR to the time point when it recovered to grade 1 or lower, which is a necessary condition to start the next cycle, was 25.5 (22 to 29) days in the 1.4 mg/m^2 group and 24.0 (15 to 27) days in the 2.0 mg/m^2 group. In addition, from the results of analysis on correlation between the C_{max} and AUC_{0-t} values on Day 1 of Cycle 1 and the hematological parameters, the possibility was suggested

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that the greater the C_{max} and AUC_{0-t} values, the greater the amount of decrease in white blood cell count and neutrophil count.

CONCLUSION:

In a total of 15 Japanese patients with solid tumors, E7389 was administered at doses of 0.7, 1.0, 1.4 and 2.0 mg/m^2 to 3, 3, 6 and 3 patients, respectively, to investigate the safety, pharmacokinetics, and if possible, antitumor activity.   DLTs occurred in 2 out of 6 patients in the 1.4 mg/m^2 group and 3 out of 3 in the 2.0 mg/m^2 group, and AEs regarded as DLT were neutrophil count decreased and febrile neutropenia.   Based on these results, it was estimated that the MTD of E7389 in Japanese patients with solid tumors would be 2.0 mg/m^2 and the RD for phase II studies would be 1.4 mg/m^2.

From the results of investigation on the pharmacokinetics of E7389, it was revealed that E7389 is a drug with low clearance and high distribution and is slowly eliminated ($t_{1/2}$: 36.4 to 59.9 hours).   Since 5.01 to 12.88% of a dose was excreted in the urine as unchanged form, it was suggested that the contribution of renal clearance to the elimination was small.   Although the C_{max} and AUC_{0-t} values increased with the increase in dose within a dose range of 0.7 to 2.0 mg/m^2, the dose proportionality could not be assessed accurately.

Regarding antitumor activity, PR (partial response) was observed in 3 patients in the 1.4 mg/m^2 group, suggesting the efficacy of E7389.   Consequently, it was considered that the antitumor activity of E7389 should also be investigated in the future, along with a detailed investigation concerning the safety.

Date of the report: August 21, 2008 (date of the original report written in Japanese)

2. SYNOPSIS

Name of Sponsor Company: Eisai Ltd.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
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Title of Study: An open-label, parallel group study to explore the pharmacokinetics of eribulin mesylate (E7389) in patients with advanced solid tumors and normal or reduced hepatic function according to the Child-Pugh system		
Study Number: E7389-E044-108		
Investigator: Professor J. H. M. Schellens		
Study center: 2 centers in The Netherlands		
Study Period: From: 12 February 2008 (first patient in) To: 6 March 2009 (end of Study Phase)		**Clinical Phase:** 1

Objectives:
Primary: to study the influence of hepatic impairment on plasma pharmacokinetic parameters of eribulin following a single IV administration of eribulin mesylate (E7389)
Secondary: to explore the safety and tolerability of eribulin mesylate among patients with reduced hepatic function

Methodology:

Study Design: Open-label. Patients were assigned to one of three groups: normal hepatic function, mild hepatic impairment (Child-Pugh A) and moderate hepatic impairment (Child-Pugh B) according to the Child-Pugh System for classifying hepatic impairment.

Study Procedures: All patients had a screening visit up to two weeks before the start of the study treatment. The Baseline tumor assessment was performed up to 28 days prior to study enrollment.
Treatment with eribulin mesylate (E7389) was given on Day 1 and the PK assessment was performed before and after study drug administration at specified time points.
A 12-lead electrocardiogram (ECG) was taken at Baseline, end of Cycle 2 and at the study termination visit.
Clinical examination and laboratory screens were performed weekly for the first two cycles, and then on Days 1 and 8 of every further cycle. If medically indicated, the assessments were performed more frequently.
Adverse events (AEs) and concomitant medications were assessed throughout the study.
Patients attended a study termination visit within 30 days after the last dose.

Pharmacokinetic Assessments: Blood samples for PK analysis were collected up to Day 7 post-dose during Cycle 1.

Efficacy Assessments: Tumor assessments were performed at screening and at appropriate clinical intervals according to the center's usual practice. The investigator assessed and documented the best response to treatment with eribulin mesylate according to RECIST criteria. Since this report only contains Cycle 1 data (the Study Phase) and efficacy assessments were not included in this primary analysis (no tumor assessments were performed in Cycle 1), these data will be reported separately.

Safety Assessments: A physical examination, vital signs and laboratory assessments were performed at screening and on days 1, 8 and 15 of each cycle. An ECG was performed at screening, at the end of

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	cycle 2 and termination visit. Information on adverse events (AEs) and concomitant medication use was collected from the time informed consent was signed.
Other Assessments:	A blood sample was taken to assess the CYP3A4 and CYP3A5 phenotype for each individual using a haplotyping approach.

Number of Patients: 18 evaluable patients (6 per group) planned.

This report provides data on 17 patients (6 Normal, 7 Child-Pugh A, and 4 Child-Pugh B) who had completed Cycle 1 at the cut-off date for the primary analysis. There were 11 males (64.7%) and 6 females, aged between 50 and 70. All patients were White.

Although 6 patients were planned to be enrolled in each group, there were actually 7 patients included in the Child-Pugh A group. After 5 patients had been enrolled in the Child-Pugh A group, the Investigator screened 2 patients with normal hepatic function. Both patients later deteriorated and no longer met the normal criteria but, instead, were assigned to the Child-Pugh A category.

Due to the challenges of identifying and recruiting suitable Child-Pugh B patients, 4 patients with moderate impairment (Child-Pugh B) were enrolled and completed Cycle 1 evaluations at the cut-off date for the primary analysis. One additional patient with moderate hepatic impairment (Child-Pugh B) was subsequently enrolled and is ongoing; data from this patient are not included in this report but will be reported separately.

Diagnosis and Criteria for Inclusion: Patients ≥ 18 years of age with histologically or cytologically confirmed advanced solid tumors that had progressed following standard therapy or for whom no standard therapy existed (including surgery or radiation therapy) with either normal hepatic function, mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B).

Test Product, Dose and Mode of Administration, Lot Number, Expiry Date:

Eribulin mesylate (E7389) injected directly as an IV bolus over 2-5 minutes or diluted in up to 100 ml 0.9% sodium chloride for IV infusion over 2-5 minutes.

   Patients with normal hepatic function received a dose level of 1.4 mg/m^2.

   Patients with mild hepatic impairment (Child-Pugh A) received a dose level of 1.1 mg/m^2

   Patients with moderate hepatic impairment (Child-Pugh B) received a dose level of 0.7 mg/m^2

Lot number: N0500764 (expiry date: 27 October 2009)

Reference Product, Dose and Mode of Administration, Lot Number, Expiry Date:

Not applicable

Duration of Treatment: PK assessments were performed during Cycle 1. Patients benefiting from eribulin mesylate treatment continued treatment beyond cycle 1. Patients remained on treatment until they had disease progression or unacceptable toxicity led to patient withdrawal. Patients attended a follow-up visit 30 days after the last dose. This report provides information on the primary study analysis, based on data from Cycle 1 of treatment for each patient. Data from subsequent cycles will be reported separately.

Criteria for Evaluation:

Pharmacokinetics: Eribulin PK parameters $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, CL and V_{ss} were derived from plasma concentrations by non-compartmental analysis.

Genotyping: Genotypes of CYP3A4 and CYP3A5 were used to classify patients as extensive, intermediate or poor metabolizers

Efficacy: A best response according to RECIST was documented by the investigator for each patient. These data will be reported separately.

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Safety: Adverse events were graded according the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3. The incidence of adverse events, out-of-normal-range laboratory safety test variables, and abnormal 12-lead ECG and physical examination findings were derived along with changes from baseline in laboratory safety test variables and vital signs measurements. Concomitant medications were also summarized.

Statistical Methods:

Pharmacokinetics: All parameters were tabulated and summarized by hepatic function category. Log transformed dose-normalized $AUC_{0-\infty}$ and C_{max} were subject to an analysis of variance (ANOVA) appropriate for the study design. The initial ANOVA model included terms for hepatic impairment category, patient age, weight and sex that were considered as covariates. Each covariate (age, weight and sex) was added one at a time, and simultaneously. Covariates that were not statistically significant and did not improve the model fit, as defined by -2 log likelihood and Akaike's Information Criterion, were dropped. Comparisons were made between each group of patients with impaired hepatic function (ie, Child-Pugh A and B) and normal controls. The treatment effect estimates obtained from the ANOVA model were back-transformed to obtain estimates for the ratios of Child-Pugh hepatic function relative to normal hepatic function. Results were presented in terms of the geometric least square means and ratios (impaired hepatic function to normal hepatic function) with associated 90% CI.

Genotyping: An exploratory analysis of patient's CYP3A phenotype with exposure to eribulin was conducted.

Efficacy: These data will be reported separately.

Safety: Data were summarized by hepatic function and study day, as appropriate, but there was no formal statistical analysis.

RESULTS

Pharmacokinetics: Patients with normal hepatic function received an IV dose of eribulin mesylate of 1.4 mg/m^2, patients with mild hepatic impairment (Child-Pugh A) received a dose of 1.1 mg/m^2, and patients with moderate hepatic impairment (Child-Pugh B) received a dose of 0.7 mg/m^2. Mean plasma concentrations of eribulin over time appear to be similar across all doses (Figure 1S).

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Figure 1S: Mean Eribulin Plasma Concentration-Time Profile Following a Single IV Administration of Eribulin Mesylate

Hepatic impairment decreased clearance (CL), prolonged the elimination half-life, and increased both AUC and C_{max} of eribulin (Table 1S).

Table 1S: Mean (SD) Pharmacokinetic Parameters for Eribulin: Pharmacokinetic Population

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

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Mean dose-normalized eribulin C_{max} was comparable between patients with normal hepatic function and patients with mild hepatic impairment 1.15 [90% CI 0.827-1.59]). Moderate hepatic impairment increased $C_{max,}$ which was 1.48-fold (90% CI 1.01-2.17) that in patients with normal hepatic function. Hepatic impairment increased exposure to eribulin. In patients with mild and moderate hepatic impairment, mean dose-normalized $AUC_{(0-\infty)}$ increased 1.75-fold (90% CI 1.16-2.65) and 2.79-fold (90% CI 1.72-4.51), respectively, compared to that in patients with normal hepatic function. Similarly, mean dose-normalized $AUC_{(0-t)}$ was 1.70-fold (90% CI 1.15-2.50) and 2.38-fold (90% CI 1.52-3.73), respectively. (Table 2S).

Table 2S: Relative Bioavailability of Eribulin Following Single IV Administration of Eribulin Mesylate to Patients with Normal Hepatic Function and Patients with Mild or Moderate Hepatic Impairment: Pharmacokinetic Population

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

a: Ratio of treatment means was Impaired: Normal
Data were normalized to a dose of 1 mg

Genotyping: All 17 patients were carriers of the CYP3A4 *1/*1 genotype, and were therefore classified as CYP3A4 extensive metabolizers. Most patients (16/17) were CYP3A5 poor metabolizers, as expected in this cohort since the most common form of CYP3A5 in Caucasians is the *3/*3 form, which creates a non-active enzyme. Thus, there was no sequence variability in CYP3A4 and very little sequence variability in CYP3A5 in this study population.

Efficacy: Efficacy assessments were not included in this primary analysis, and will be reported separately.

Safety: All patients (17/17) experienced at least one TEAE. The majority of patients (13/17) experienced at least one AE reported to be treatment-related (probably or possibly related): normal group (4/6), Child-Pugh A (6/7), and Child-Pugh B (3/4). The highest incidences of TEAEs reported to be treatment-related were alopecia (7/17), nausea (5/17), and fatigue (4/17). Given the small numbers of patients, there were no apparent differences in distribution of AEs or treatment-related AEs across all groups. One patient (Child-Pugh B) experienced peripheral sensory neuropathy, reported as probably treatment-related, which resolved after a dose delay of 7 days. A total of three patients (one in each group) experienced neutropenia, reported as probably treatment-related, which resolved; only one patient required a dose reduction. Two of the three incidences of neutropenia were graded as CTCAE 3 or 4 (one Grade 3 and one Grade 4). There were no deaths, life-threatening SAEs, or SAEs reported as treatment-related. Two hepatic impaired patients had SAEs requiring hospitalization, although these were not reported as related to study drug. No patients withdrew from study treatment during the Study Phase (Cycle 1 through to Day 1 of Cycle 2). There were no obvious hematologic or

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other laboratory abnormalities, and no obvious patterns in the laboratory data between the different hepatic function groups. There were no obvious changes in vital signs and no evidence of any differences between the hepatic function groups. There were no clinically significant ECG abnormalities noted in the opinion of the Investigator. Seven patients changed ECOG performance status category between screening and Cycle 2 Day 1, and 10 patients remained unchanged (neither worsened nor improved).

CONCLUSIONS:

- Hepatic impairment affects the disposition of eribulin:
  - Hepatic impairment decreased clearance and prolonged the elimination half-life of eribulin.
  - Mean dose-normalized eribulin C_{max} was comparable between patients with normal hepatic function and patients with mild hepatic impairment (ratio estimate 1.15 [90% CI 0.827-1.59]). Moderate hepatic impairment increased C_{max}, which was 1.48-fold (90% CI 1.01-2.17) that in patients with normal hepatic function.
  - Hepatic impairment increased exposure to eribulin. In patients with mild and moderate hepatic impairment, mean dose-normalized $AUC_{(0-\infty)}$ was 1.75-fold (90% CI 1.16-2.65) and 2.79-fold (90% CI 1.72-4.51), respectively, compared to that in patients with normal hepatic function. Similarly mean dose-normalized $AUC_{(0-t)}$ was 1.70-fold (90% CI 1.15-2.50) and 2.38-fold (90% CI 1.52-3.73), respectively.
- There was no sequence variability in CYP3A4 and very little sequence variability in CYP3A5 observed in this study population. These results suggest that there was unlikely to be any contribution of sequence variability in the CYP3A family of enzymes to the observed variability in eribulin exposure that was associated with hepatic impairment in this study.
- Eribulin mesylate was generally well tolerated in all groups. All patients experienced at least one TEAE and the majority of patients experienced at least one AE reported to be treatment-related. There were no deaths, life-threatening SAEs, or SAEs reported as treatment-related. There appeared to be no differences between hepatic impairment groups with respect to safety parameters in this study where the dose was prospectively adjusted in consideration of reduced hepatic function. However, the patient numbers in each group were too small to draw conclusions about specific events.
- Thus, hepatic impairment increases exposure to eribulin. This effect is more pronounced for moderate hepatic impairment.

Date of the Report: 21 January 2010

2   SYNOPSIS

Name of Sponsor Company: Eisai Limited	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
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Title of Study: An Open-Label, Phase I Study to Evaluate the Pharmacokinetics and Tolerance of Co-administration of Oral Multiple Dose of Ketoconazole and an IV (bolus) Infusion of Eribulin in Patients with Advanced Solid Tumors

Study Number: E7389-E044-109

Investigator: Professor Jan H. M. Schellens, MD, PhD

Study center: The Netherlands Cancer Institute, Department of Medical Oncology, Antoni van Leuwenhoek Hospital, Amsterdam, The Netherlands

Study Period: 18 February 2009 (first patient in) to 13 July 2009 (date when the last patient completed Cycle 1).	Clinical Phase: Phase 1

Objectives:

Primary: To study the influence of repeated oral administration of ketoconazole, a potent CYP3A4 inhibitor, at a therapeutic dose on the plasma pharmacokinetics (PK) of eribulin administered by intravenous (IV) infusion.

Secondary: To assess the safety and tolerability of eribulin when co-administered with oral ketoconazole, and to further explore the safety and tolerability of eribulin when given alone on Days 1 and 8 of a 21-day schedule in patients with solid tumors.

Methodology: Study Design:	This was a randomized, open-label, 2-treatment, 2-sequence, 2-way crossover study in patients with solid tumors. In Cycle 1 patients were randomly allocated to one of two treatment sequences (Group 1 or Group 2):

- Group 1 received eribulin mesylate on Day 1 followed by eribulin mesylate plus ketoconazole on Day 15 and ketoconazole alone on Day 16

- Group 2 received eribulin mesylate plus ketoconazole on Day 1, ketoconazole alone on Day 2 followed by eribulin mesylate on Day 15

After PK assessments in the first cycle (study phase), patients could continue to receive eribulin mesylate at a dose level of 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle (extension phase). This CSR reports the results from the Study Phase only; results from the extension phase will be reported separately.

Study procedures: All patients had a Screening visit up to 2 weeks before the start of study treatment. The Baseline tumor assessment was performed up to 28 days prior to beginning study treatment. Treatment with eribulin mesylate (E7389) was given on Day 1 and Day 15, and the PK assessments were performed before and after study drug administration, and at specified time points.

A 12-lead electrocardiogram (ECG) was taken at Screening and Study Termination. An ECG was also planned for the end of Cycle 2.

Clinical laboratory tests (hematology, clinical chemistry and urinalysis were

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	performed at screening (within 72 hours), on Days 1, 7, 15, and 21 of Cycle 1, and Days 1, 8 and 15 of each subsequent cycle, and at Study Termination. From Cycle 3 onwards, Day 15 assessments were only required if clinically indicated. A urine pregnancy test was performed at Screening and Day 1 of Cycle 1 (if applicable).
	Complete physical examinations were completed at Screening, on Days 1, 7, and 15 of Cycle 1, and on Day 1 of subsequent cycles. Symptom directed physical examinations were performed at other visits if clinically indicated.
	Vital signs, including temperature, blood pressure and heart rate, were measured at Screening (within 72 hours), and on Days 1, 7, 15, and 21 of Cycle 1, and Days 1, 8 and 15 of each subsequent cycle, and at Study Termination. From Cycle 3 onwards, Day 15 assessments were only required if clinically indicated.
	Adverse events (AEs) and concomitant medications were assessed throughout the study. Patients attended a study termination visit within 30 days after the last dose.
Pharmacokinetic Assessments:	Intensive PK blood sampling was performed following administration of eribulin mesylate (with and without ketoconazole) on Days 1 and 15. Group 1 received ketoconazole on Days 15 and 16, and Group 2 received ketoconazole on Days 1 and 2. Collection of blood samples for determination of eribulin (free base) plasma concentrations occurred during the first cycle of treatment only.
Efficacy Assessments:	For tumor assessment, at a minimum, radiological scans of relevant anatomical areas were to be performed at Baseline. Thereafter scans were to be performed at appropriate clinical intervals according to the center's usual practice only in those areas where disease was found at Baseline, and at any other new areas of suspected disease; or sooner if there was evidence of progressive disease.
Safety Assessments:	Safety variables assessed during study visits consisted of the following: occurrence of AEs (including SAEs), concomitant medication usage, and changes in physical examination findings, clinical laboratory test results, vital signs, ECG evaluations, and Eastern Cooperative Oncology Group (ECOG) performance status.
Other Assessments:	A blood sample was taken to assess the CYP3A4 and CYP3A5 phenotype for each individual using a haplotyping approach.

Number of Patients:	Number of patients planned: 12 Number of patients enrolled: 12 Number of patients analyzed for pharmacokinetics: 10 Number of patients analyzed for safety: 12

Diagnosis and Criteria for Inclusion: Patients at least 18 years of age who had a histologically or cytologically confirmed advanced solid tumor that had progressed following standard therapy or for which no standard therapy existed (including surgery or radiation therapy).

Test Product: Eribulin mesylate was provided as a sterile injectable solution in vials containing 1.0 mg eribulin mesylate in 2 mL solution containing ethanol/water (5:95).

Dose: Group 1: 1.4 mg/m^2 on Day 1 and 0.7 mg/m^2 on Day 15 in Cycle 1. 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle thereafter.

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Group 2: 0.7 mg/m^2 on Day 1 and 1.4 mg/m^2 on Day 15 in Cycle 1. 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle thereafter.

Mode of Administration: The eribulin mesylate solution could be injected directly as an IV bolus over 2 to 5 minutes or diluted in up to 100 mL 0.9% sodium chloride solution for IV infusion over 2 to 5 minutes.

Lot Number: N0500764 **Expiry Date:** 27 October 2009

Co-administered Product: Ketoconazole 200 mg tablet (Trade Name Nizoral made by Janssen Cilag).
Dose: Group 1: 200 mg on Days 15 and 16 of Cycle 1   Group 2: 200 mg on Days 1 and 2 of Cycle 1
Mode of Administration: Oral, administered 1 hour before and 23 hours after eribulin mesylate dosing.
Lot Number: 76C2J00 **Expiry Date:** 30 September 2012

Duration of Treatment: The first treatment cycle (study phase) lasted 28 days. Patients who benefited from eribulin mesylate treatment during the first cycle could continue to receive eribulin mesylate at a dose of 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle until they had progressive disease, lost clinical benefit due to toxicity, refused further therapy, withdrew consent, or the Investigator concluded that further therapy was not in the best interest of the patient.

Criteria for Evaluation:

Pharmacokinetics: Blood samples for PK assessments were obtained pre-dose and at specified intervals up to 144 hours after dosing with eribulin mesylate on Days 1 and 15. The following eribulin PK parameters were derived from plasma concentrations by non-compartmental analysis: the dose-normalized area under the concentration-time curve from zero (pre-dose) extrapolated to infinite time ($AUC_{0-\infty}$), the area under the concentration-time curve from zero (pre-dose) to time of last quantifiable concentration (AUC_{0-t}), the maximum observed plasma concentration (C_{max}), the time of maximum observed plasma concentration (t_{max}), the half-life ($t_{1/2}$), clearance (CL) and volume of distribution at steady state (V_{ss}).

Safety: Adverse events (AEs) were monitored and recorded throughout the study. Physical examination, vital signs and laboratory safety tests were performed weekly in Cycle 1, on Days 1, 8 and 15 of Cycle 2, on Days 1 and 8 of each subsequent cycle, and at study termination, or more frequently if medically indicated. An electrocardiogram (ECG) was taken at Screening, end of Cycle 2 and at Study Termination.

Efficacy: Tumor assessments were performed at Baseline, and thereafter between Day 15 and Day 21 of the treatment cycle at appropriate clinical intervals according to the study site's usual practice, or sooner if there was evidence of disease progression. A best response according to Response Evaluation Criteria in Solid Tumors (RECIST) was documented by the Investigator for each patient. Only data for Cycle 1 of treatment (Study phase) is presented in this report. Only patients showing progressive disease (PD) according to RECIST during or at the end of Cycle 1 will be reported here.

Genotyping: CYP3A4 and CYP3A5 phenotype was predicted for each patient by haplotyping.

Statistical Methods:

Pharmacokinetics: All patients who completed the PK evaluations on Days 1 to 7 and Days 15 to 21 were included in the PK evaluable population. Analysis of PK parameters used an estimation approach based on mean ratio (i.e. the magnitude of the interaction) and confidence intervals (CIs). Log transformed dose-normalized $AUC_{0-\infty}$ and C_{max} were subjected to an analysis of variance (ANOVA) appropriate for the study design. The ANOVA model included terms for treatment, period (day) and patient. Comparisons were made between eribulin in the presence of ketoconazole (test) and eribulin alone (reference).

Safety: All patients who were enrolled and received at least a partial dose of study treatment were

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included in the safety population. The incidence of AEs, out of range laboratory safety test values, abnormal 12-lead ECGs and physical examination findings were summarized along with changes from Baseline in laboratory safety test variables and vital signs measurements. Concomitant medications and Eastern Cooperative Oncology Group (ECOG) assessments were also summarized.

Efficacy: Patients with Baseline measurable disease as per RECIST who received at least a partial dose of study treatment were included in the analysis set for response. The best overall response was listed and summarized using summary statistics but there was no formal statistical analysis. For the purposes of this report (reporting data for Cycle 1 only), patients with PD according to RECIST during or at the end of the first cycle were to be listed.

Genotyping: The relationship between CYP3A predicted phenotypes (both CYP3A4 and CYP3A5) and eribulin exposure was investigated, but no formal statistical analysis was planned.

RESULTS

Pharmacokinetics:

Ketoconazole had no effect on eribulin clearance (CL) and elimination half-life. The mean elimination half-life of eribulin was 45.6 hours when administered alone and 40.5 hours when co-administered with ketoconazole. Ketoconazole co-administration had no effect on AUC and C_{max} of eribulin. Mean eribulin pharmacokinetic parameters are summarized in the table below.

Mean (SD) Pharmacokinetic Parameters for Eribulin mesylate Administered Alone or Co-administered with Ketoconazole: Pharmacokinetic Population

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

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

Eribulin exposure when eribulin mesylate was administered alone was bioequivalent to eribulin exposure

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when co-administered with ketoconazole (ratio of geometric least square means: 0.95, 90% CI 0.80, 1.12). The ratio of treatment means for C_{max} showed bioequivalence between eribulin + ketoconazole and eribulin only (ratio of geometric least square means: 0.97, 90% CI 0.83, 1.12).

Genotyping:

All 10 patients assessed for genotyping were extensive metabolizers for CYP3A4 and poor metabolizers for CYP3A5. $AUC_{0-\infty}$ and C_{max} results are the same as those presented for dose-normalized data in the table above.

Efficacy:

Extension Phase data are not presented in this CSR and will be reported separately.

Safety:

All patients (12/12) experienced at least 1 treatment emergent adverse event (TEAE). All patients (12/12) experienced at least 1 AE reported to be treatment related (probably or possibly related): 10/12 patients during exposure to eribulin mesylate alone, and 6/10 when exposed to eribulin mesylate + ketoconazole. The most frequently reported treatment related TEAEs were fatigue, nausea, and neutropenia, each reported by 4/12 patients.

Nausea and fatigue were the most common TEAEs, each reported by 6/12 patients. The highest incidence of TEAEs was seen in the SOC of gastrointestinal disorders (10/12), followed by general disorders and administration site conditions (9/12).

There were no deaths, life threatening SAEs, or SAEs reported as treatment related. 2 patients experienced SAEs which required hospitalization, although these were not reported as related to study drug. One patient withdrew from the study due to TEAEs. Five patients experienced CTCAE Grade 3 or 4 events that were reported as treatment related.

There was no consistent trend in changes from Baseline for any hematology parameter. A trend towards an increase in mean change from Baseline over time for ALT was observed for Group 1 which was not seen in Group 2. In addition, a trend towards a mean decrease in change from Baseline over time for lactate dehydrogenase was observed for Group 1 - again not seen in Group 2. No other obvious patterns in laboratory data between the groups were identified.

No new safety concerns were identified during this study and the safety results from this study are consistent with the known safety profile of eribulin.

CONCLUSIONS:

- Co-administration of ketoconazole had no effect on single-dose exposure to eribulin.
- Eribulin mesylate was generally safe and well tolerated.
- No new safety concerns were identified during this study and the safety results from this study are consistent with the known safety profile of eribulin.

Date of the Report: 2 February 2010

2.   SYNOPSIS

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Title of Study: An Open-Label, Multicenter, Single Arm QT Interval Prolongation Study of Eribulin Mesylate (E7389) in Patients with Advanced Solid Tumors
Study Number: E7389-E044-110
Investigator: Thierry Lesimple, MD
Study center: 5 centers in France.

Study Period: From: 24 February 2009 (first patient in) To: 22 July 2009 (end of Study phase)	**Clinical Phase:** Phase 1

Objectives:
Primary: To assess whether eribulin mesylate (E7389), when administered on Days 1 and 8 of a 21-day cycle in patients with solid tumors, has an impact on the ECG, with focus on cardiac repolarization, as measured by QT/QTc interval, as well as through a pharmacokinetic-pharmacodynamic (PK/PD) analysis.
Secondary: To further characterize the pharmacokinetic (PK) profile of eribulin mesylate; to further explore the safety and tolerability of eribulin mesylate; to assess best overall response using RECIST criteria in patients with measurable disease (note efficacy has not been analysed for the current CSR/synopsis).

Methodology:

Study design:
This was an uncontrolled, open-label, multi-centre, single-arm phase I study to determine the effect of eribulin mesylate on cardiac repolarization in patients with solid tumors. The study consisted of three phases: Pre-treatment Phase (up to 28 days), Study Phase (3 weeks) and Extension Phase (unlimited duration). Pre-treatment included Screening and Baseline. The Study Phase included intensive cardiac and PK assessment during Cycle 1 of therapy. The Extension Phase evaluated efficacy/safety and additional cardiac assessments. Subjects were to receive eribulin mesylate until subject discontinuation from study therapy occurred, for the reasons specified below. Patients who demonstrated clinical benefit could continue treatment for as long as clinical benefit was sustained.

Study Procedures and assessments:
For each patient, Screening evaluation was performed up to 28 days (between -28 to -1 days) prior to administration of eribulin mesylate (except for the baseline bone scan which could be performed up to 6 weeks before treatment). Treatment with eribulin mesylate (1.4 mg/m^2 IV bolus given over 2-5 minutes) was administered in the morning on Days 1 and 8 of a 21-day Study Phase (Cycle 1). On these days, repeat continuous ECG digital Holter recordings and triplicate 12-lead ECGs were obtained and blood samples for PK analysis were collected pre-infusion and post-infusion at specific time-points. These timepoints coincided with the ECG timepoints at end of eribulin mesylate infusion, 15 min, 30 min, 1, 1.5, 2, 3, 4, 5, 6 and 10, 24 and 48 hours after eribulin mesylate administration. Specific clinical chemistry assessments were performed on Days 1, 2, 3, 8, 9 and 10 to coincide with the ECG assessments, and on Day 15. Hematology and liver function tests were performed on Days 1, 8 and 15. Other safety assessments (adverse events [AEs], serious adverse events (SAEs), vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, physical examination),

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concomitant medications and tumor response were assessed throughout the study. Patients were required to have a study termination visit within 30 days after the last eribulin mesylate dose. Patients continued to receive treatment with eribulin mesylate on Days 1 and 8 of each 21-day cycle for all subsequent cycles (part of the Extension phase, not reported here). Patients benefiting from treatment continued to receive eribulin mesylate beyond Cycle 1 until one of the criteria listed in the protocol for removal of patients from therapy or assessment (listed below under "duration of treatment") occurred.

Number of Subjects:
   • Number of patients planned: 22 evaluable patients
   • Number of patients screened: 31 patients (there were 5 screen failures)
   • Number of patients enrolled and received study treatment: 26 patients
   • Number of patients analyzed for safety: 26 patients
   • Number of patients analyzed for ECG, PK and PK/PD evaluations: 26 patients
   • Number of patients analyzed for efficacy: efficacy was not reported as only Cycle 1 data focusing on ECG and PK/PD evaluations was analyzed for the current CSR

Diagnosis and Criteria for Inclusion: Patients of at least 18 years of age who had a histologically or cytologically confirmed advanced solid tumor that had progressed following standard therapy or for which no standard therapy existed (including surgery or radiation therapy). Patients had to have a sinus rhythm and QRS < 120msec. Exclusion criteria included the following criteria that are relevant to the ECG evaluation in this study: patients with marked baseline prolongation of QT/QTc interval (QTc interval > 500 msec); with a history of additional risk factors for torsades de pointes (TdP; e.g., heart failure, cardiac ischemia, recent myocardial infarction [MI], family history of Long QT Syndrome); with uncontrolled metabolic disorders (e.g. hypokalemia, hypercalcemia and hypomagnesemia) at entry to the study; patients treated with antiarrythmic drugs or other medications that prolongued the QT/QTc, that could not be discontinued prior to entry into the study phase; patients with implantable pacemaker or automatic implantable cardioverter defibrillator (AICD); bradycardia (defined as <50 beats/minute); personal history of unexplained syncope within the last year prior to entry into the study, and patients with other significant disease or disorders that, in the Investigator's opinion, should have excluded the patient from the study.
Test Product: eribulin mesylate (E7389) Eisai Standard 1.0 mg (as mesylate salt) in 0.1 mL ethanol plus 1.9 mL Water for Injection. **Dose:** eribulin mesylate at a dose of 1.4 mg/m^2 on Day 1 and Day 8 over a 21-day cycle. **Mode of Administration:** eribulin mesylate was to be administered as an IV bolus over 2 to 5 minutes. **Lot Number:** N0600720; **Expiry Date:** 24 October 2010
Reference Product, Dose and Mode of Administration, Lot Number, Expiry Date: Not applicable
Duration of Treatment: The first treatment cycle lasted 21 days. Patients benefiting from eribulin mesylate treatment during the first cycle could continue to receive eribulin mesylate until one of the following occurred: progressive disease; loss of clinical benefit due to toxicity; withdrawal of consent; presence of other medicinal conditions that prohibited continuation with therapy; pregnancy; failure of the subject to comply with study procedures which compromised safety; delay of more than 14 days in starting the next cycle due to toxicities; presence of new medical information that warranted the

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termination of the study; termination of the study by the Sponsor for safety reasons; or the Investigator concluded that further therapy was not in the best interest of the subject.

Criteria for Evaluation:

Cardiac assessments

For each patient, the effect of eribulin mesylate on cardiac repolarization was evaluated by standardized 12-lead ECG recording retrieved from continuous Holter and digital ECG as follows:

1. Single 12-lead ECG at least 96 hours prior to day of first treatment administration in order to establish eligibility criteria for QT/QTc interval (must be ≤ 500msec).

2. Triplicate 12-lead ECGs extracted from the continuous Holter were collected on Cycle 1, Day 0. The extractions were based on hypothetical time-matched start and end times of infusion (for pre-dose and end of infusion time points).

3. Triplicate 12-lead ECGs were extracted in a 2-min window prior to Infusion Start Time, and as close as possible to this time, from the continuous Holter recordings at pre-dose, and end of eribulin mesylate infusion on Days 1 and 8 of Cycle 1.

4. Triplicate 12-lead ECGs were extracted from the continuous Holter recordings at 15 min, 30 min, 1, 1.5, 2, 3, 4, 5, 6 and 10 hours in a 2-min window prior to PK blood sample collection, after the start of eribulin mesylate administration on Days 1 and 8 of Cycle 1. Triplicate 12-lead ECGs were collected just prior to PK blood sample collection at 24 hours (i.e., Day 2 and 9 of Cycle 1) and 48 hours (i.e., Day 3 and 10 of Cycle 1) after start of eribulin mesylate administration, respectively.

5. Triplicate 12-lead ECGs taken 5 minutes apart were taken pre- and post-eribulin mesylate infusion during the extension phase cycles.

Pharmacokinetics: Blood samples for PK analysis were collected from all subjects at the same timepoints as ECG collection during the Study Phase (Cycle 1).

Safety: Adverse events (AEs) and concomitant medications were assessed throughout the study. A complete physical examination was performed at screening, Day 1 of the Study Phase (Cycle 1) and Extension Phase, and at Study Termination. Symptom-directed physical exams were performed on Days 8 and 15 of the Study Phase and within the Extension Phase as clinically indicated. Laboratory assessments were performed at Screening, on every visit day and at Study Termination. Urinalysis was performed at Screening, Day 1 of Cycle 1 and Study Termination. Standard 12-lead ECG was collected at Screening, at Day 2, 3, 8, 9 of Study Phase, and at pre-dose and post-dose of Day 1 and Day 8 of each extension phase cycles. Eastern Cooperative Oncology Group (ECOG) performance status was recorded at Screening and at Cycle 1 (Day 1), Cycle 2 (Day 1) and Study Termination.

Efficacy: Tumor assessments were performed at Screening and at appropriate clinical intervals according to the centers' usual practice, or sooner if there was evidence of disease progression. A best response according to Response Evaluation Criteria in Solid Tumors (RECIST) was documented by the Investigator for each patient. These data will be reported separately.

Statistical Methods:

ECG:

All ECG analyses were performed on the Per Protocol Population, which consisted of all patients in the safety analysis set who did not have any major protocol violations or deviations and had evaluable ECG data. The principal goal of ECG analyses was to evaluate the effect of eribulin mesylate on the ECG with a

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focus on cardiac re-polarization as measured by QT/QTc intervals and by comparing ECG results obtained before and after study drug administration. QT was corrected primarily using Fridericia's formula (QTcF) and also using Bazett's formula (QTcB), defined as:

- QTcF is the length of the QT interval corrected for heart rate by Fridericia's formula:
- $QTcF = QT/(RR)^{0.33}$
- QTcB is the length of the QT interval corrected for heart rate by Bazett's formula:
- $QTcB = QT/(RR)^{0.5}$

At each time point where triplicate ECG readings were obtained, the average of the three measurements was to be used.

Analysis of primary endpoint: mean time-matched, baseline corrected QTcF:

To characterize the effect of erbulin mesylate on QTcF prolongation, summary statistics were provided for the primary endpoint based on the per protocol (PP) population. No formal statistical test was conducted. Mean and its one-sided 95% confidence interval (CI) for change of QTcF from time-matched baseline was calculated at each pre-selected post-dosing time point on Day 1 and Day 8: pre-dose (Day 8 only), end of infusion, 15 minutes, 30 minutes, 1, 1.5, 2, 3, 4, 5, 6, 10 hours. To further study the potential QTcF prolongation signal observed from the 95% CIs for mean, the correlation between QTcF and plasma concentration was modeled. In addition, as supportive analysis the number and percentage of patients whose post-treatment QTcF values, or whose change in QTcF from Baseline, were in excess of limit values listed below, were summarized by measurement occasion. The purpose of this analysis was to highlight clinically noteworthy intervals and changes from baseline. This analysis included all post-baseline QTcF values that were measured during Study Phase.

QTcF interval prolongation:
>30-60 msec change from baseline
>60 msec change from baseline

Newly observed abnormal QTcF values on treatment:
>470 msec
>500 msec

Analysis of Secondary ECG Endpoints:

Secondary ECG endpoints included the following:
- QTcF change from baseline at time (t_{max}) of observed maximal plasma concentration (C_{max}), HR, PR, QRS, QT and QTcB intervals.
- U-wave and T-wave.

Secondary ECG endpoint analysis was based on Holter ECG measurements. Actual values and changes

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from baseline for QTcF at t_{max}, HR, PR, QRS, QT and QTcB intervals were summarized through basic summary statistics for the following time points on Day 1 and Day 8: pre-dose (Day 8 only), end of infusion, 15 minutes, 30 minutes, 1, 1.5, 2, 3, 4, 5, 6, 10 hours. The same analyses planned for QTcF were performed for QTcB. U-wave and T-wave morphologies were identified and presented as follows:

- U-wave: present or absent
- T-wave: normal or abnormal (e.g Flattened, inverted, biphasic and notched)

Categorical summaries were provided for U-wave and T-wave at each time point.

Pharmacokinetics: the PK population consisted of all subjects who had received at least one dose of study medication, and had sufficient plasma concentration data to facilitate the calculation of pharmacokinetic parameters. PK analysis of plasma eribulin concentrations was conducted using non-compartmental analysis by The Netherlands Cancer Institute (NKI), using a fully validated scintillation counting liquid chromatography tandem mass spectroscopy (LC/MS/MS) assay. Eribulin pharmacokinetic parameters $AUC_{(0-48hrs)}$, C_{max} and t_{max} were derived from plasma concentrations by non-compartmental analysis based on actual sample time. Descriptive statistics were computed. Additionally, C_{max} was summarized across patients and treatment days using a linear mixed effects model on log-transformed data, in order to provide the estimate of mean C_{max} associated with therapeutic exposure to eribulin, for derivation of the effect on QTc associated with therapeutic concentrations.

The concentration-QTc relationship was assessed using a linear mixed effects analysis of the relationship between baseline-adjusted QTcF interval (ΔQTcF) and observed eribulin concentration, according to the equation: $\Delta QTcF = \alpha + \beta*$ [eribulin], where inter-individual variability was estimated for both intercept (α) and slope (β). The effect of treatment period (i.e. Day 1 or Day 8) on slope and intercept was also evaluated. (Note: QTcF=QT/(RR)0.33, where RR is unitless and QT is in milliseconds. RR can be calculated as 60/(heart rate)).

Additionally, in a complementary PK/PD analysis, the relationship between QTcF/QTcNi and eribulin concentration was assessed using linear mixed effect modeling to estimate the maximal change (mean and upper 95% confidence limit) in the baseline-adjusted QTc associated with therapeutic concentrations of eribulin. QTcNi was derived from each individual's QT/RR slope at Baseline.

Safety: All enrolled patients who received at least one dose of study medication and who had at least one safety assessment following the first dose of study medication were included in the safety population. With the exception of ECG analyses, which were based on Per Protocol Population, all other analyses described on this section were based on the Safety Analysis Set. The incidence of AEs, out of range laboratory safety test values, abnormal 12-lead ECGs and physical examination findings were summarized along with changes from baseline in laboratory safety test variables and vital signs measurements. Concomitant medications were also summarized.

Efficacy: These data will be reported separately.

RESULTS:

Patient Population:

- A total of 31 patients from 5 investigational centers were enrolled in this study; of these, 26 patients received study treatment, and 24 patients completed the Study phase.
- Two patients were discontinued from the study before completion of the Study phase, due to AE and

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progression of disease (note that a third patient did not receive study drug on cycle 1 Day 8 due to AE, but subsequently recovered from AE and resumed treatment on Cycle 2 Days 1 and 8).

- For the purpose of the study, 26 patients were evaluable for cardiac and PK assessment. The population consisted of 13 males and 13 females aged between 28 and 79 years (mean 55.9 years). Cancer diseases included a wide range of tumors such as lung, colorectal, breast, head and neck, prostate, and sarcoma. Almost all were with metastatic disease and heavily pre-treated. Relevant medical history included hypertension (n=6), hypothyroidism (n=3) and diabetes (n=2). Six patients were also previously exposed to anthracycline or anthracenedione therapy. None of the 26 patients in the study had any history of other cardiovascular diseases.

12-Lead ECG Holter/Digital Evaluations:

- On Day 1, QTcF mean changes from the time-matched baseline were close to zero, indicating no difference between Cycle 1 Day 1 and the time-matched baseline. Time-matched predose QTcF on this day was 4 msec and the largest mean baseline adjusted QTcF post-dosing of eribulin was 2 msec at 15 minutes. A QTcF effect exceeding 8 msec or lower could be excluded at all time points post-dosing of eribulin (Figure 1S).
- On Day 8, the changes from baseline were larger and the variability substantially higher, resulting in wider confidence intervals (Figure 1S). Time-matched pre-dose QTcF on Day 8 was 9 msec and all post-dose QTcF intervals varied +/-3 msec around the pre-dose value, ranging from 6 to 11 msec. The largest mean baseline-adjusted QTcF post-dosing of eribulin was 11 msec at 15 minutes and at 6 hours. A QTcF effect exceeding 20 msec or lower could be excluded at all time points post-dosing of eribulin.
- Therefore, there was a time-dependent effect on the QTcF interval, which was prolonged before and after dosing on Day 8 in Cycle 1, as compared to Day 1. The largest observed mean QTcF changes from baseline on Days 1 and 8 were 2 msec and 11 msec, respectively.
- Women have been reported at a high risk of prolonged QT. Therefore, time-matched QTcF change from baseline was also analyzed by gender. On Day 8, the time-matched QTcF change from baseline varied between 9 and 18 msec in women and between -2 and 7 msec in men. As expected, the observed QTcF differences appeared to be somewhat larger in women. However, the small number of subjects precludes any firm conclusions based on this observation.
- Likewise, a sub-analysis of time-matched QTcF change from baseline by prior anthracycline use was also performed. This analysis did not reveal any pronounced differences between patients with or without prior exposure to anthracycline. Again, the small number of subjects (n=6) previously exposed to anthracycline precludes any firm conclusions.
- On both Day 1 and 8, the heart rate was reduced compared to nominal time points at baseline during the first 1.5 hours post eribulin dosing. This could signify differences from baseline in either resting state or autonomic tone.
- The upward shift of QTcF values on Day 8 is also reflected in a small increase in the number of categorical outliers: During Day 1, there were no patients with QTcF interval durations of 470-500 msec or >500 msec. During Day 8, one patient had a QTcF 470-500 msec at several post-eribulin mesylate infusion timepoints. Eribulin mesylate was not discontinued for this patient and the QTcF elevation resolved spontaneously. No patients had a QTcF interval value >500 msec.

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- During Day 1, 5 patients had a change of >30-≤60 msec observed post-eribulin dosing for 48 hours. During Day 8, 10 patients had changes from baseline in QTcF of >30-≤60 msec post-infusion and only one patient had a mean change from baseline in QTcF of >60 msec. None of these subjects had cardiac SAEs or were discontinued due to cardiac-related events. Three patients who experienced an elevated QTcF interval also experienced cardiac AEs (one Grade 2 vasovagal episode [coded as presyncope]; Grade 1 vertigo episode [dizziness]; Grade 1 atrial fibrillation). None of these events were considered related to study drug by the investigator.
- The effect on QTcF on Cycle 1 Day 8 was not seen in all patients; it was driven by approximately 10 patients who had large changes as opposed to the majority of patients who experienced small changes (comparable to Day 1), including negative changes. Note that for the 10 patients, the QTcF changes returned to baseline at the start of Cycle 2 Day 1. The changes occurred in the context of electrolyte disturbances, adverse events such as nausea, vomiting, diarrhea, insufficient food intake/anorexia, and differences in concomitant medications between Day 1 and Day 8.

Figure 1S   Mean and One-side 95% CI of QTcF Change from Baseline vs time profile (Per Protocol Population)
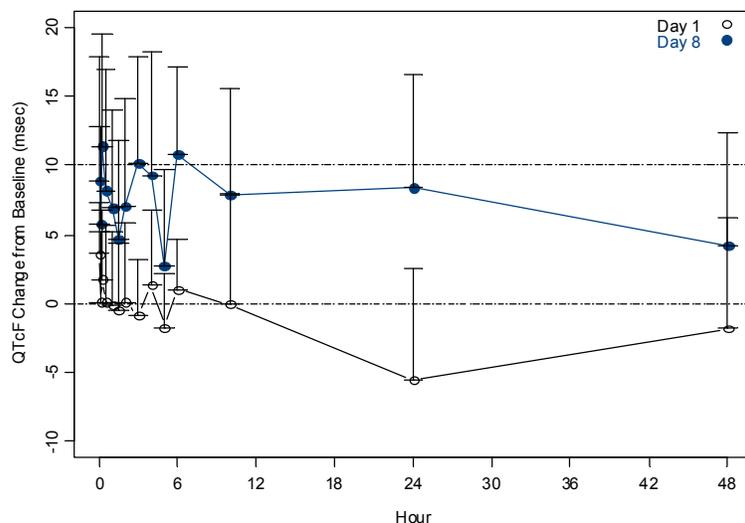
Pharmacokinetic and Pharmacokinetic/Phamacodynamic Analyses:

Patients received a dose of 1.4 mg/m^2 eribulin mesylate on Days 1 and 8 of a 21-day Study Phase (Cycle 1). Mean plasma concentrations of eribulin over time were similar across Days 1 and 8, which is consistent with data from previous studies. Eribulin exposure was comparable on Days 1 and 8.

The PK parameters after the start of eribulin mesylate infusion are presented in Table 1S:

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Table 1S   **PK Parameters Following IV Administration of 1.4 mg/m^2 Eribulin Mesylate on Day 1 and Day 8 to Patients with Solid Tumors (Pharmacokinetic Population)**

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

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

In a complementary PK/PD analysis, the relationship between QTcF/QTcNi and eribulin concentration was assessed using linear mixed effect modeling to estimate the maximal change (mean and upper 95% confidence limit) in the baseline-adjusted QTc associated with therapeutic concentrations of eribulin mesylate.

Exposure to eribulin was similar on Day 1 and Day 8. The exploratory graphical analyses of QTcF demonstrated that there was no relationship between mean baseline adjusted QTcF and eribulin plasma concentration. A clear difference between Day 1 and Day 8 baseline adjusted QTcF values was however observed, where Day 8 was almost 8 msec higher despite no difference in mean eribulin concentrations between the days. When an individualized heart rate correction algorithm was applied, the QTc increase from Day 1 to 8 was smaller than with QTcF; around 5 msec.

In summary, a small increase of the QTcF interval emerged from Day 1 to Day 8 in Cycle 1 of this study in cancer patients with advanced disease. This effect was unrelated to the plasma concentration of eribulin mesylate and unrelated to any known metabolites. When an individualized heart rate correction algorithm (QTcNi) was applied, the increase of the QTc interval was smaller, which may suggest that QTcF was not an appropriate correction method in this population. A delayed drug effect cannot be excluded, but other factors may either have contributed or may have caused the observed QTc prolongation independently. Such factors include electrolyte disturbances, adverse events such as nausea, vomiting, diarrhea, insufficient food intake/anorexia, or differences in concomitant medications between Day 1 and Day 8.

Efficacy: these data will be reported separately.
Safety:
- All patients (26/26) experienced at least one TEAE during the Study phase. The majority of patients (24/26) experienced at least one AE reported to be treatment-related (probably or possibly).

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- No TEAEs leading to study treatment dose reductions were reported. One patient did not receive the Cycle 1 Day 8 dose, which was recorded as a dose-interruption, due to a TEAE of CTC Grade 4 neutropenia, reported to be probably treatment related.
- The highest incidences of TEAEs reported to be treatment-related were neutropenia (13/26), asthenia (11/26), leucopenia (8/26), and nausea (8/26).
- A total of 13 patients (13/26) experienced at least one episode of neutropenia during the Study phase; all episodes were reported to be probably related to study treatment except for one episode, which was reported to be possibly related to study treatment. The Cycle 1 Day 8 dose of study treatment was reported to be interrupted due to the TEAE of neutropenia for one patient but the dose of study treatment was not changed for the other 12 patients reported to have treatment-related neutropenia. At the time of data cut-off the majority of patients (9/13) had recovered or were recovering from their TEAE of neutropenia. Eleven of the 13 patients reported to have treatment-related neutropenia were CTC Grade 3 or 4 (5 were Grade 3 and 6 were Grade 4).
- During the study, no AEs were reported as related to ECG. Four patients experienced 5 AEs of interest (presyncope [2 events], tachycardia, vertigo and atrial fibrillation). The vasovagal episodes and presyncopes reported could not be attributed to a proarrhythmic event. Noteworthy, all mean QTc values at any time were below 450 msec, and all events were considered not related to study drug.
- There were no deaths during the Study Phase. There were 14 treatment-emergent SAEs, the majority were considered unrelated to study medication.
- One patient withdrew from study medication during the Study Phase due to the Grade 3 SAE of renal failure which was considered "probably related" to study drug.
- There were no obvious hematologic or other laboratory abnormalities.
- There were no obvious changes in vital signs and no noticeable worsening of the ECOG status.

CONCLUSIONS:
- No relationship was found between eribulin concentration and ΔQTcF in this study.
- Day 1 QTcF values were generally unchanged from Baseline with mean changes around zero and upper confidence interval bounds below 10 msec for all time-points.
- The QT prolongation on Day 8 was 8 msec for QTcF and 5 msec for individually corrected QTcNi. A delayed drug effect cannot be excluded, but other factors such as nausea, vomiting, diarrhea, and electrolyte disturbances may have caused or contributed to the small, observed QTc prolongation. A QTc prolongation of this size is not expected to be of clinical concern in this patient population.
- Four patients experienced 5 AEs of interest (presyncope [2 events], tachycardia, vertigo and atrial fibrillation). The vasovagal episodes and presyncopes reported could not be attributed to a proarrhythmic event. Noteworthy, all QTc values at any time were below 450 msec, and all events were considered not related to study drug.
- Erybulin mesylate demonstrated an acceptable safety profile. No new or unexpected toxicities were reported in this study.

Date of the Report: 17 Feb 2010

2. STUDY SYNOPSIS

Title of Study: A Phase II Open-Label Study of E7389 (Halichondrin B Analog) in Patients with Advanced/Metastatic Breast Cancer Previously Treated with Chemotherapy Including an Anthracycline and a Taxane.

Coordinating Investigators: Linda Vahdat, MD, Weill Cornell Breast Center, New York, NY; Joanne Blum, MD, Sammons Cancer Center, Dallas, TX.

Study Centers: 23 study centers in the United States.

Publications:

Blum J, Forero L, Heiskala MK, Meneses N, Chandrawansa K, Fang F, Shapiro G, Silberman S, Vahdat L. E7389, a novel anti-tubulin, in patients with refractory breast cancer. 2006 ASCO Annual Meeting 24: No 18S, Abstract 653.

Blum JL, Pruitt B, Fabian CJ, Rivera RR, Shuster DE, Meneses NL, et al. Phase II study of erbulin mesylate (E7389) halichondrin B analog inpatients with refractory breast cancer. 2007 ASCO Annual Meeting 25: No. 18S, Abstract 1034.

Blum JL, Pruitt BT, Fabian CJ, Shuster DE, Meneses NL, Chandrawansa K, Fang F, Vahdat L. Phase II study of eribulin mesylate (E7389) in patients with heavily pretreated advanced breast cancer (Study number E7389-A001-201). 2007 ASCO BSC Abstract 223.

Amended CSR History: This report is based on the original CSR (Date of Report 04 Dec 2008) and the CSR Addendum (Date of Report 28 Apr 2009) Revisions specified in the CSR addendum have been incorporated into this amended CSR.

Studied Period: November 12, 2004 (FPI) through November 1, 2006 (LPO)	**Clinical Phase:** Phase II

Objectives:

Primary:

1) To determine the response rate to E7389 monotherapy administered as an intravenous (IV) bolus of 1.4 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle, and on Days 1 and 8 of a 21-day cycle in patients with advanced/metastatic breast cancer treated with chemotherapy including an anthracycline and a taxane, with previously documented progression during or within 6 months following the last dose of prior chemotherapy.

Secondary:

1) To evaluate safety and tolerability of E7389 monotherapy
2) To evaluate antitumor activity of E7389 as determined by duration of response, time to progression, and overall survival
3) To evaluate quality of life (QOL) as measured by the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire, tumor-related symptom improvement or worsening measured by pain intensity on a visual analog scale (VAS), analgesics consumption, weight changes, and Eastern Cooperative Oncology Group (ECOG) performance status.
4) To evaluate tumor pharmacogenetics and their possible relationship to response (assessment of beta-tubulin isotype mRNA on biopsy sample).

Methodology:

This open-label, single-arm, multi-center study of E7389 enrolled 104 patients with advanced metastatic breast cancer previously treated with an anthracycline and a taxane. Eligibility for study entry was confirmed at a screening visit. E7389 was administered after pre-dose safety and tumor evaluations were completed. Additional consent was required to allow pharmacogenetic analysis of available diagnostic biopsy samples. Two cohorts of patients were enrolled. The first cohort (N=71) received E7389 on Days 1, 8, and 15 of a 28-day cycle. Because of the high number of dose delays, reductions or omissions due to neutropenia on Day 15, a second cohort (N=33) was added to the study to receive E7389 on Days 1 and 8 of a 21-day cycle. Both

cohorts received E7389 as an IV bolus at a dose of 1.4 mg/m^2. Patients returned to the study site every week for scheduled safety assessments. Adverse events (AEs) were monitored and recorded throughout the study. An electrocardiogram (ECG) was to be done prior to drug administration, at approximately the time of maximum drug concentration (Cmax) after the first treatment, and at study termination. Patients kept an analgesic consumption diary, completed a FACT-B questionnaire, and evaluated their pain intensity on a VAS. Tumor assessments were performed according to the Response Criteria in Solid Tumors (RECIST) at baseline, every two cycles and whenever there was clinical evidence of disease progression.

Number of Patients: Number of evaluable patients planned: 86
Number of patients enrolled: 104
Number of patients analyzed for efficacy: 87
Number of patients analyzed for safety: 103

Diagnosis and Criteria for Inclusion:
Female patients at least 18 years of age with histologically or cytologically confirmed advanced metastatic breast cancer that was not amenable to curative therapy (either surgery or radiation therapy). Patients were to have had measurable disease by RECIST and received prior treatment with an anthracycline and a taxane. Patients were to have progressed within 6 months of the last dose of chemotherapy, or experienced disease progression while receiving chemotherapy for advanced/metastatic disease. Patients were to have had a life expectancy of $\geq$ 3 months, adequate renal, liver and bone marrow function, and no clinically significant therapy-related toxicity at study entry.

Test Product: E7389 was provided as a 500 μg/mL solution in ethanol/water (5:95)
Dose: 1.4 mg/m^2
Mode of Administration: IV bolus administration
Batch No.s: ESG-001, ESG-002, ESK-001

Duration of Treatment: Patients remained on study treatment until they had progression of disease, no longer had clinical benefit, experienced unacceptable toxicity that led to study withdrawal, or they withdrew or were withdrawn for any other reason.

Reference Therapy, Dose, Mode of Administration, Batch No(s): None

Criteria for Evaluation:
Efficacy: response rate, duration of response, time to progression, and overall survival

Safety: occurrence of AEs, serious AEs (SAEs), changes in physical examination findings, clinical laboratory test results, vital signs and ECG evaluations.

Quality of Life: quality of life (FACT-B), ECOG performance status, and pain recorded on VAS.

Pharmacogenetics: The relative expression levels of various beta-tubulin isoforms including beta-III, beta IVb, beta-V and beta VI, as well as stathmin and MAP4 in the tumors of the patients were correlated with sensitivity to E7389 on the basis of patients' responses to treatment.

Statistical Methods: For the 28-day treatment cycle, Simon's optimal two-stage design was used. Hypotheses tested were the null hypothesis H$_0$:Response Rate $\leq$ 12% versus the alternative H$_a$:Response Rate $\geq$ 25%. In Stage 1 of the 28-day cycle treatment group, the drug was tested on 19 evaluable patients. The study was to be terminated if $\leq$ 2 patients responded with complete response (CR) or partial response (PR), otherwise the study was to enroll at least 42 additional patients into that cohort (Stage II). Summary statistics for the efficacy and safety data were provided for each treatment cohort and for the two cohorts combined. Patients who met the key enrollment criteria of measurable disease that had progressed within 6 months of prior chemotherapy treatment (per protocol population) were included in the primary efficacy evaluation. Overall survival, progression-free survival, and duration of response were summarized using Kaplan Meier estimates. Summary statistics for the clinical benefit and safety endpoints were provided. Safety analysis was based on the safety population.

SUMMARY – CONCLUSIONS:
RESULTS:

Efficacy:
- E7389 demonstrated anti-tumor activity in the patients in this study.
- The overall response rate based on independent review was 11.5%. The response rate was comprised solely of PR; there were no patients with CR. The overall response rates for the 28-day and 21-day schedule cohorts separately were 10.2% and 14.3%, respectively. The clinical benefit rate (PR + stable disease [SD] ≥ 6 months) was 17.2%. Median duration of response was 171 days (5.6 months). The overall response rate based on investigator assessment was 16.5%, including one patient with CR.
- Median progression-free survival was 79 days based on the independent review. The 12-week progression-free survival rate was 46.1%, and was slightly higher in the 21-day schedule group (52.8%) than in the 28-day schedule group (43.4%). The 6-month progression-free survival rate was 25.9% for the two cohorts combined, with the 21-day treatment group having a numerically higher rate (33.9%) than the 28-day treatment group (22.6%).
- Median overall survival was 275 days (9.0 months). The 6-month overall survival rate was 67.8%, and the 1-year overall survival rate was 45.7%. The 1-year survival rate was higher in the 21-day schedule group (60.7%) than in the 28-day schedule group (38.4%).
- E7389 demonstrated activity across all identified subgroups of patients; the response rate was higher in less heavily pre-treated patients (3 or fewer prior chemotherapy regimens).

Safety:
- SAEs were reported for approximately one third of the patients in this study. Grade 4 and Grade 5 AEs were reported for 37% and 4% of patients, respectively. One treatment-related Grade 5 AE was reported (neutropenic sepsis).
- The most common study drug-related AE was neutropenia (75%). Grade 3/4 neutropenia and febrile neutropenia occurred in 64% and 4% of patients, respectively. Two patients developed neutropenic sepsis; one of these patients died with neutropenic sepsis (SAE). Other common treatment-related AEs were fatigue (53%), alopecia (41%), nausea (37%), and anemia (36%); most of these events were Grade 1 or 2 and none were Grade 4.
- Treatment-related peripheral neuropathy occurred in 31% of patients. Grade 3 neuropathy occurred in 5% of patients, and no Grade 4 neuropathy was reported.
- Seven patients (6.8%) died while on treatment or within 30 days of their last treatment. Nine patients (8.7%) discontinued the study due to an AE.
- Dose interruptions, delays or omissions were needed for 65% of patients (76% of patients in the 28-day schedule group and 42% of patients in the 21-day schedule group). Dose reductions occurred in 18% of study patients.
- There were no clinically meaningful changes in mean chemistry, vital signs, physical examination findings, or ECG parameters, including QT interval.

Quality of Life:

The mean change from baseline in TOI was similar for responders (patients who had a best response of PR) and non-responders. However, 57% of responders showed an increased QOL, as measured by an increase in TOI of 5 points or more, compared with 45% of non-responders. No patients in the responder subset showed deterioration of QOL, while 11% of the study population overall showed a deterioration of QOL. This suggests that QOL may be improved in patients who have objective positive tumor response to E7389 treatment..

Tumor Pharmacogenetics:
- The pharmacogenetics data provided some supporting evidence for possible associations of the pair

BTcIII and Stathmin with overall survival, of the pair MAP4 and BTcIII with progression-free surival, and of BTcIVb with tumor response.

- Of these gene expression levels, only the association of BTcIII with overall survival showed potential statistical significance ($p = 0.050$ when assessed jointly with other covariates, and $p = 0.005$ when assessed individually). BTcIII was negatively associated with overall survival.

CONCLUSIONS:

- The administration of E7389 at a dose of 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle had an acceptable tolerability profile, with neutropenia, fatigue, and alopecia being the most common, treatment-related AEs.
- E7389 demonstrated anti-tumor activity in heavily pre-treated patients with advanced/metastatic breast cancer. Subanalyses showed that the response rate and clinical benefit rate were higher among hormone receptor-positive patients. The activity of E7389 was dependent upon the number of prior chemotherapy regimens; the response rate was 23% for patients who had received three or fewer regimens compared to 7% for those with four or more regimens.
- E7389 retained activity among patients who had received multiple prior chemotherapies, including an anthracycline, a taxane, and capecitabine.
- Taken together, these findings support a favorable risk benefit assessment for the use of E7389 in the treatment of women with heavily pretreated, advanced breast cancer.

Date of the Report: 12-Feb-2010

2.   STUDY SYNOPSIS

Title of Study: A Phase II Open Label Single-Arm-Study of E7389 in Patients With Locally Advanced or Metastatic Breast Cancer, Previously Treated With Anthracycline, Taxane, and Capecitabine Therapy, Refractory to the Last Prior Therapy for Their Disease.

Coordinating Investigator: Mary Ann Allison, MD, Comprehensive Cancer Centers of Nevada, Henderson, NV

Study Centers: Multicenter

Publications:

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

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

Amended CSR History: This report is based on the original CSR (Date of Report 12 JAN 2009) and the CSR Addendum (Date of Report 12 MAY 2009). Revisions specified in the CSR addendum have been incorporated into this amended CSR. In addition, population PK data in Table 20 were revised and clarified. Final estimates were converted relative to those from the EMF Consulting report, and the same conversion needed to be applied to the standard error on the estimate (SEE) and 95% CI.

Studied Period: 28-OCT-2005 (first patient in) through 01-SEP-2007 (data cut-off)	**Clinical Phase:** Phase II

Objectives:

Primary: To evaluate the efficacy and safety of E7389 in patients with locally advanced or metastatic breast cancer who have received anthracycline, taxane, and capecitabine as prior therapy, and are refractory to their last chemotherapy regimen, documented by progression on or within 6 months of therapy.

Secondary: To investigate the pharmacokinetic/pharmacodynamic (PK/PD) relationships in a population pharmacokinetic (PK) study.

Methodology:

This open-label, single-arm, multi-center Phase II study was conducted in breast cancer patients. Radiologic scans to evaluate disease status were performed every two cycles and if there was clinical evidence of disease progression. To maintain uniformity of tumor assessment, an independent, blinded review of radiographic images was performed for all dosed patients, except those determined by study investigators to have progression on or before their Cycle 2 scan. Tumor assessments were performed according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Number of Patients: Number of evaluable patients planned: up to 300
Number of patients enrolled: 299
Number of patients analyzed in the primary efficacy analysis: 269
Number of patients analyzed for safety: 291

Diagnosis and Criteria for Inclusion:

Female patients at least 18 years of age with histologically or cytologically confirmed advanced metastatic breast cancer that was not amenable to curative therapy (either surgery or radiation therapy). Patients were to have had measurable disease by RECIST and received at least two and not more than five prior chemotherapy regimens including an anthracycline, a taxane and capecitabine. Patients were to have progressed while on, or within 6 months of, the last regimen of chemotherapy for advanced disease. Patients were to have had a life expectancy of $\geq$ 3 months, adequate renal, liver and bone marrow function, and no clinically significant therapy-related toxicity at study entry.

Test Product: E7389 was provided as a 500 μg/mL solution in ethanol/water (5:95)
Dose: 1.4 mg/m^2 on Days 1 and 8 every 21 days.
Mode of Administration: 2 – 5 minute intravenous (IV) bolus administration
Lot Numbers: ESH-001, N0500232 (XD41A1 and XD41A2), and N0500442 (XD41A3 and XD41A4).

Duration of Treatment: Patients remained on study treatment until they had progression of disease, no longer had clinical benefit, experienced unacceptable toxicity that led to study withdrawal, or withdrew or were withdrawn for any other reason.

Reference Therapy, Dose, Mode of Administration, Batch No(s): None

Criteria for Evaluation:

Efficacy: response rate, duration of response, overall survival and progression-free survival.

Safety: occurrence of adverse events (AEs), serious adverse events (SAEs), changes in physical examination findings, clinical laboratory test results, vital signs and electrocardiogram (ECG) evaluations.

Quality of Life (QOL) endpoints: QOL assessments using the European Organization for Research on the Treatment of Cancer (EORTC) QOL questionnaire, and tumor-related symptoms assessment using Eastern Cooperative Oncology Group (ECOG) performance status, pain (visual analogue scale), and analgesic consumption.

PK/PD: Sparse PK sampling was conducted and samples were analyzed for 209 patients, during the first treatment cycle only. Population analysis was used to characterize the pharmacokinetic profile of E7389. Appropriate nonparametric or parametric methods were used to examine the PK/PD relationships of E7389.

Statistical Methods: Analysis of the objective response rate was based on the best overall response as determined by the independent review. A one-sided binomial test was used to test the null hypothesis objective response rate of less than or equal to 15%. Kaplan-Meier plots were provided for overall survival, progression free survival, and duration of response. The EORTC QOL questionnaire was summarized at each measurement occasion through graphical displays, summary statistics, and percent frequencies of response. Repeated measures analysis of variance models were used to evaluate the change in scores over time. Tumor-related symptom assessments were based on change from baseline in ECOG performance status, pain and analgesic use. At each assessment, patients were classified as improved, no change, or worsened.

SUMMARY – CONCLUSIONS:
RESULTS:
Efficacy:

- The overall response rate by independent review was 9.3% (95% CI: 6.1, 13.4), all responses are partial responses (PR).
- The overall response rate by investigator assessment was 14.1% (95% CI: 10.2, 18.9), with one complete response (CR).
- The clinical benefit rate (PR + stable disease [SD] ≥ 6 months) by independent review was 17.1% (95% CI: 12.8, 22.1).
- Median duration of response was 126 days (95% CI: 89, 177) (4.2 months).
- Median progression-free survival was 79 days (95% CI: 64, 92). The 12-week progression-free survival rate was 45.9% (95% CI: 39.8, 52.1), and the 6-month progression-free survival rate was 15.6% (95% CI: 10.7, 20.5). [2]
- Median overall survival was 315 days (10.3 months). The 6-month overall survival rate was 72.3%.
- E7389 demonstrated activity across all identified subgroups of patients. The response rate, clinical benefit rate and progression-free survival were higher among hormone receptor-positive patients. E7389 demonstrated activity in patients who were refractory to prior therapy with an anthracycline, a taxane, or capecitabine.

Safety:

- The most frequently reported E7389-related AEs were asthenia/fatigue (64.9%), alopecia (60.1%), neutropenia (59.8%), and nausea (44.3%). Grade 4 neutropenia occurred in 32% of patients, and

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[2] This conclusion was revised by addendum.

febrile neutropenia occurred in 5.5% of patients. The frequency of Grade 3/4 AEs was < 3% for all toxicities other than hematologic, asthenia/fatigue, and peripheral neuropathy.

- Treatment-related peripheral neuropathy occurred in 24.1% of patients. Grade 3 neuropathy occurred in 5.5% of patients, and no Grade 4 neuropathy was reported. Pre-existing neuropathy did not appear to be exacerbated by study treatment.
- SAEs were reported for approximately 88/291 patients (30%) in this study. Study drug-related SAEs were reported for 39/291 patients (13.4%); the most common drug-related SAEs were neutropenia/febrile neutropenia.
- One patient death was considered by the investigator to be possibly related to study treatment (unexpected death of unknown cause); other deaths were considered not related to study treatment.

Quality of Life:

Exploratory analysis of QOL parameters indicated symptomatic improvement of disease among patients whose tumors were controlled by E7389 therapy.

PK and PK/PD Analysis:

- PK of E7389 was best described by a three-compartment model. The IV infusion was described by a zero-order constant infusion, over 0.07 hours in the population, with between-subject variability of 94.1%.

- The population mean clearance was 2.98 L/h , approximately half covarying with renal function, the other half related to liver function. The between-subject variability on clearance was 57.4%. Clearance decreased when aspartate transaminase (AST) values were greater than the upper limit of normal (ULN) range. Body weight and body surface area (BSA), age, sex, race, baseline ECOG, and coadministration of CYP3A inhibitors did not affect E7389 clearance.

- Volume of distribution of the central compartment was close to the volume of blood at 3.72 L and no between-subject variability was estimated. Volume of distribution of the peripheral compartments was 3.60 L and 126 L, with respectively 97.9% and 51.5% coefficient of variation between subjects. The body size covariates, including body weight and BSA, age, sex and race were not shown to influence E7389 volumes of distribution.

CONCLUSIONS:

- The administration of E7389 at a dose of 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle had an acceptable tolerability profile, with asthenia/fatigue, alopecia, neutropenia, and nausea being the most common treatment-related AEs.
- E7389 has anti-tumor activity in this heavily pretreated patient population who had received a median of 4 prior chemotherapy regimens including an anthracycline, a taxane, and capecitabine. Response rate determined by independent review for the eligible population was 9.3% (95% CI: 6.1, 13.4%). However, the study did not meet the protocol specified efficacy criterion of an overall response rate of >15% in this patient population.

Date of the Report: 25Feb2010

2.   SYNOPSIS

Name of Sponsor Company: Eisai Limited	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Not Applicable	Volume:	
Name of Active Ingredient: Eribulin mesylate	Page:	

Title of Study: 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.
Study Number: E7389-G000-305
Principal Investigators: Prof Chris Twelves and Dr Linda Vahdat.
Study centers: This was a multi-center study conducted in a total of 135 centers in 19 countries (Argentina, Australia, Belgium, Brazil, Canada, Croatia, Czech Republic, France, Germany, Hungary, Italy, Poland, Russia, South Africa, Spain, Switzerland, Turkey, United Kingdom, and the United States).

Study Period: The study began on 16 November 2006 (first patient entered) and the data cut-off was 12 May 2009. The last date of enrollment was in November 2008.	**Clinical Phase:** Phase 3

Objectives: **Primary**: To compare the overall survival (OS) of patients treated with E7389 versus the Treatment of Physician's Choice (TPC) (including anti-tumor treatment of the Investigator's choice and palliative treatment) in patients with locally recurrent or metastatic breast cancer, who had received 2 to 5 prior chemotherapy regimens, which must have included an anthracycline and a taxane 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 (6) months of therapy. Human epidermal growth factor receptor 2 (HER2/*neu*) positive patients could have been treated with trastuzumab in centers where this treatment was available, and estrogen receptor-positive tumors could have been treated with anti-hormonal therapy. **Secondary:** To compare Progression Free Survival (PFS) between the two treatment groups. Objective Tumor Response Rate (ORR) as measured using Response Evaluation Criteria in Solid Tumors (RECIST) criteria and Duration of Response in each treatment group. Furthermore, safety parameters (adverse events [AEs], laboratory parameters, concomitant medication, and study drug exposure) for all patients.
Methodology: This was a multi-center, Phase 3, open-label, randomized, study in advanced breast cancer patients who had received two to five prior chemotherapy regimens, which had to include an anthracycline and a taxane as prior therapy unless contraindicated. At least two regimens had to have been given for locally recurrent or metastatic disease. Patients were randomized in a 2:1 ratio to receive either eribulin or the TPC. The TPC was defined as any single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer; or palliative treatment or radiotherapy, administered according to local practice. Treatment with another investigational agent in the TPC group was not allowed. Tumor assessments were performed for all patients at 8-weekly intervals (+/- 1 week) irrespective of the treatment group. Follow-up for survival was assessed every three months after discontinuation of treatment. All AE and concomitant medication data were collected for all patients throughout the study, irrespective of the treatment arm. All other assessments, specified in the study protocol flowchart, applied to patients in the eribulin group only. Patients randomized to receive TPC were assessed according to standard practice for the chosen treatment.

Name of Sponsor Company: Eisai Limited	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
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Name of Active Ingredient: Eribulin mesylate	Page:	

Number of Patients:
- Number of patients planned: Up to approximately 1000.
- Number of patients randomized: 762 (508 eribulin, 254 TPC)
- Number of patients analyzed for efficacy (Intent-to-Treat [ITT] population): 762 (508 eribulin, 254 TPC)
- Number of patients analyzed for safety (patients that received treatment) : 750 (503 eribulin, 247 TPC)

Diagnosis and Criteria for Inclusion: Female patients, aged ≥18 years, with locally recurrent or metastatic breast cancer who had received two to five prior chemotherapy regimens, which had to contain an anthracycline and a taxane component, at least two of which had to be given for locally recurrent or metastatic disease. Patients had to prove refractory to the most recent chemotherapy, documented by progression on or within six months of that therapy. In addition, patients with known HER2/*neu* positive tumors might have been previously treated with trastuzumab in centers where this treatment was available, and patients with known estrogen receptor (ER) positive disease might have been treated with anti-hormonal therapy. Patients for whom HER2/*neu* status, ER, and progesterone receptor status were unknown were accepted into the study.
Previous chemotherapy, radiation, trastuzumab or hormonal therapy must have been discontinued three weeks before administration of eribulin or TPC.

Test Product: Eribulin mesylate was provided as a 0.5 mg/mL solution in ethanol/water (5:95).
Dose and Mode of Administration: 1.4 mg/m^2 IV bolus administration was given over 2 to 5 minutes on Days 1 and 8 every 21 days.

Reference Product: TPC
Dose and Mode of Administration: According to local practice

Duration of Treatment: Patients remained on study until one or more of the following occurred: Disease progression as assessed by clinical evaluation or as documented by RECIST, lost clinical benefit because of undue toxicity, patient withdrawal of consent, Investigator concluded that further therapy was not in the best interest of the patient, the presence of other medical conditions that prohibited continuation with therapy, pregnancy, the failure of the patient to comply with study procedures compromising safety, a delay of more than 14 days in starting the next cycle due to toxicities, or the presence of residual toxicities that in the opinion of the Investigator prohibited further administration of treatment, the presence of new medical information that warranted the termination of the study, or termination of the study by the Sponsor.

Criteria for Evaluation:
Efficacy Assessments: OS, PFS, ORR, and duration of response according to RECIST.
Safety Assessments: AEs, serious adverse events (SAEs), concomitant medications, laboratory assessments (chemistry, hematology, and urinalysis), vital signs, physical examination, Eastern Cooperative Oncology Group Performance Status, and electrocardiograms.

Statistical Methods:
The primary analysis of OS was compared between eribulin and the TPC group in the ITT Population using a two-sided stratified log-rank test at a nominal significance level of 0.049 (adjusted for the interim analysis). Patients were stratified by HER2/*neu* status, prior capecitabine treatment, and geographical region. The secondary efficacy endpoints analyzed were PFS, ORR, and duration of response. Kaplan-Meier plots and the Kaplan-Meier estimates of the medians, and first and third quartiles were presented with the 95% confidence intervals for OS, PFS, and duration of response. Tumor response was evaluated according to the RECIST guidelines, modified as per the protocol (Appendix 8 of the protocol). ORR was analyzed using exact Pearson Clopper 2-sided 95% confidence limits for the tumor response rates in each group. The efficacy endpoints of PFS, ORR, and duration of response were assessed according to Investigator and Independent assessment. Sensitivity analyses of these assessments were also performed.
Exploratory subgroup analyses could have been performed for OS, PFS, and ORR, in subgroups of patients depending on whether there were sufficient numbers of patients within each subgroup at the end of the study.
Summary statistics for AEs, laboratory parameters, and other safety parameters were provided for the safety population.

Name of Sponsor Company:	Individual Study Table	(For National Authority Use Only)
Eisai Limited	Referring to Part of the Dossier	
Name of Finished Product:		
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Eribulin mesylate	Page:	

The primary analysis was planned to occur when 411 events (deaths) had been recorded. An interim analysis (blind to Investigators and the sponsor) was performed after 50% of the deaths had been observed.

RESULTS

Key efficacy results are summarized in the Table below. Subgroup analyses showed a consistent trend in favor of eribulin across a wide variety of patient subpopulations.

Efficacy Parameter	Eribulin	TPC
Overall Survival (ITT Population)	**(n = 508)**	**(n = 254)**
Number of Events	274	148
Median (95% confidence interval [CI]) days	399 (360, 434)	324 (282, 380)
Hazard Ratio, eribulin: TPC (95% CI) (stratified Cox proportional hazards)	0.809 (0.660, 0.991)	
p-value (stratified log-rank)[a]	0.041	
Progression-free Survival[b]	**(n = 508)**	**(n = 254)**
(ITT Population)		
Median (95% CI), days	113 (101, 118)	68 (63, 103)
Overall Response Rate[b]	**(n=468)**	**(n=214)**
(Response Evaluable Population)		
% (95% CI)	12.2 (9.4, 15.5)	4.7 (2.3, 8.4)

a: Stratified by geographic region, HER2/*neu* status, and prior capecitabine therapy.
b: Based upon Independent radiographic review.

Safety

- The AE profile of eribulin in this study was consistent with previous studies with eribulin. The most common AE reported was neutropenia, and the most common AE leading to discontinuation of treatment was peripheral neuropathy. The majority of AEs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2, with the exception of neutropenia.
- A lower percentage of patients in the eribulin group (4.0%) than the TPC group (7.7%) died during study treatment, or within 30 days of their last study treatment (this includes patients who died because of disease progression). Similarly, the percentage of patients with AEs with an outcome of death (including patients who died >30 days after the last dose) was also lower in the eribulin group (4.0%) than TPC group (7.3%).
- SAEs were reported for 25.0% of eribulin-treated patients and 25.9% of patients in the TPC group. The most frequently reported SAEs in the eribulin group were febrile neutropenia (4.2%) and neutropenia (1.8%).
- AEs leading to discontinuation were reported for 13.3% of eribulin-treated patients and for 15.4% of patients in the TPC group. The most common AE that led to discontinuation of eribulin was peripheral neuropathy (4.8% of patients).
- In the eribulin group, development of Grade 3 and Grade 4 neutropenia occurred in 28.4% of patients and 28.6% of patients, respectively (AEs of Grade 3 and Grade 4 neutropenia were reported for 21.1% and 24.1% of patients, respectively). Overall, 57.1% of patients in the eribulin arm had a nadir ANC during the treatment period, and the median time to nadir was 78 days. The majority of patients recovered from the nadir (93.7%), with a median time to recovery of eight days. Neutropenia rarely led to febrile neutropenia (4.6%).
- In the eribulin group, AEs of peripheral neuropathy were reported for 34.6% of patients, 7.8% at Grade 3 and 0.4% at Grade 4. Eribulin treatment was discontinued because of peripheral neuropathy for 4.8% patients. More than half of the patients with Grade 3/4 peripheral neuropathy continued eribulin treatment. The 1 year estimate for the rate of development/progression of peripheral neuropathy was 21.4% and 9.5% with eribulin and TPC respectively, based on a Kaplan-Meier analysis.
- The safety pattern for the TPC groups in this patient population appeared to be similar to that expected for

Name of Sponsor Company: Eisai Limited	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Not Applicable	Volume:	
Name of Active Ingredient: Eribulin mesylate	Page:	

the use of these drugs.
CONCLUSIONS: Treatment with eribulin significantly prolonged OS in patients with late-stage breast cancer when compared with TPC (p=0.041). Thus, the study met its primary endpoint. The secondary endpoints of PFS and ORR were consistent with the primary endpoint; PFS was longer for the eribulin group and ORR was greater. The observed safety profile of eribulin was acceptable for a chemotherapeutic agent in late line settings and the drug was generally well-tolerated. This safety profile was consistent with that observed in Phase 2 studies.
Date of the Report: 19 March 2010

APPENDIX 4.6 CLINICAL PHARMCOLOGY AND BIOPHARMACEUTICS FILING FORM FOR NDA

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

NDA Number	201-532	**Brand Name**	Halaven
DCP Division (I, II, III, IV, V)	V	**Generic Name**	Eribulin mesylate
Medical Division	Oncology	**Drug Class**	Halichondrin B Analogue
OCP Reviewer	Stacy S. Shord, PharmD	**Indication(s)**	Locally advanced or metastatic breast cancer who previously received at least two chemotherapy regimens
OCP Team Leader	Hong Zhao, PhD	**Dosage Form**	1 mg per 2 mL intravenous sterile solution
Pharmacometrics Reviewer	Anshu Marathe, PhD	**Dosing Regimen**	1.4 mg/m^2 on days 1 and 8 of each 21-day cycle
Date of Submission	03/30/2010	**Route of Administration**	Slow intravenous bolus over 2 min to 5 min
Estimated Due Date of OCP Review	08/09/2010	**Sponsor**	Eisai Inc.
Medical Division Due Date	09/02/2010	**Priority Classification**	Priority
PDUFA Due Date	9/30/2010		

Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical comments if any
STUDY TYPE				
Table of contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular listing of all human studies	X			
HPK summary	X			
Labeling	X			
Reference bioanalytical and analytical methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		E7389-E044-103
Isozyme characterization:	X	1		DSD2003-01
Blood/plasma ratio:	X	1		E7389-E044-103
Plasma protein binding:	X	1		DSD2001-38
Pharmacokinetics (e.g., Phase I) -	X	7		NCI-5730 (dose escalation) E7389-A001-101 (dose escalation) E7389-A001-102 (dose escalation) E7389-J081-105 (RP2D) E7389-E044-108 (hepatic impairment) E7389-E044-109 (DDI) E7389-E044-110 (QTc)
Healthy Volunteers-				None
single dose:				
multiple dose:				

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Patients-				
single dose:	X	8		NCI-5730 (dose escalation)
				E7389-A001-101 (dose escalation)
				E7389-A001-102 (dose escalation)
				E7389-J081-105 (RP2D)
				E7389-E044-108 (hepatic impairment)
				E7389-E044-109 (DDI)
				E7389-E044-110 (QTc)
				E7389-G000-211 (supportive study)
multiple dose:	X	4		NCI-5730
				E7389-A001-101
				E7389-J081-105
				E7389-E044-110
Dose proportionality -				None
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		E7389-E044-109 (ketoconazole)
In-vivo effects of primary drug:				None
In-vitro:	X	9		DSD2004-03 (induction CYP1A and CYP3A)
				DDDM2005-03 (inhibition CYP2C)
				DMPK2000-13 (inhibition CYPs)
				DSD2001-31 (inhibition CYP3A)
				DSDM2001-009 (inhibition coadmin. drugs)
				DDDA2008-004 (pgp)
				CAIVT0105 (pgp)
				CAIVT0106 (pgp)
				CAVT0102 (beta-tubulin)
Subpopulation studies -				
ethnicity:	X			popPK
gender:				popPK
geriatrics:	X			popPK
renal impairment:	X			popPK
hepatic impairment:	X	1		E7389-E044-108
pediatrics:				Request waiver
PD:				
Phase 2:	X	2		E7389-A001-201
				E7389-G000-211
Phase 3:	X	1		E7389-G000-305
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3		E7389-A001-101 (ANC, fatigue)
				E7389-A001-102 (ANC, fatigue)
				E7389-J081-105 (ANC)
				E7389-E044-110 (QTc)
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	7		Pooled phase 1 (101, 102, 103, 105, 108, 109, 110) and phase 2 data (211)
Data sparse:	X	1		Pooled phase 1 (101, 102, 103, 105, 108, 109, 110) and phase 2 data (211)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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II. Biopharmaceutics				
Absolute bioavailability:				*Not applicable*
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				*Not applicable*
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
QT$_C$ studies:	X	1		E7389-E044-110
Genotype/phenotype studies	X	4		NCI-5730 (β-tubulin, MAP4, stamin)
				E7389-G000-211 (β-tubulin, MAP4, stamin)
				E7389-E044-103 (CYPs)
				E7389-E044-108 (CYP3A4)
				E7389-E044-109 (CYPs)
Chronopharmacokinetics				None
Pediatric development plan				Pediatric Waiver Request
Literature references				None
Total Number of Studies		20		11 patient / 9 *in vitro* human materials

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	All clinical studies completed using eribulin in the same formulation
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	Data sets not provided or requested
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Requested waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? <u>Yes</u>

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Provide Appendix IV of the Population PK report which contains the population pharmacokinetics base and final model control streams and output listings.

2. For the HPLC-ESI-MS/MS method described in report no. E7389\VAL\088:

    a. Provide long-term stability data of eribulin in human plasma for a minimum duration of the long-term storage of the samples collected as part of study 108, 109 and 110.

    b. Provide methods to calculate inter-day precision and accuracy.

3. For the hepatic impairment study described in report no. E7389-E044-108:

    a. Provide the data for the additional patient with moderate hepatic impairment enrolled into the study.

_____

Reviewing Clinical Pharmacologist   Date

_____

Team Leader/Supervisor   Date

NDA:	201-532/000, Original Submission	**IND:** 67,193	
Compound:	Eribulin mesylate, 1.0 mg per 2 mL intravenous sterile solution		
Sponsor:	Eisai Inc.		
Filing Date:	May 3, 2010		
Reviewer:	Stacy S. Shord, PharmD		

Background and Mechanism of Action:
Standard therapy for recurrent or metastatic breast cancer for last-line therapy, following first- and second-line treatment with appropriate chemotherapy, endocrine therapy and/or biologics, is not defined. First-line therapy provides a response rate (RR) of greater than or equal to 50%, but the cancer typically progresses. Second line therapy typically includes single agent therapy, with capecitabine the most widely used single agent, and it is the only treatment approved for treatment after an anthracycline and a taxane. The overall response rate (ORR) is 20% and the median survival is 10.1 months. Ixabepilone is the only therapy approved for last-line therapy. The ORR is 11.5% and the median survival is 8.6 months.

Eribulin mesylate (E7386) is an analogue of halichondrin B, a natural product isolated from marine sponges (*Halicohondira koadai)* and it is a non-taxane microtubule dynamics inhibitor. Eribulin mesyalte demonstrated a statistically significant and clinically relevant improvement in overall survival compared to treatment of physicians' choice (TPC) following the completion of a single phase 3 randomized clinical trial. The results of this phase 3 clinical trial are supported by two phase 2 studies in which an ORR of 13.6% (study 201) and 9.3% (study 211) was demonstrated. The proposed indication is 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.

Rationale for Phase 3 Dose Selection:
Four phase 1 dose escalation clinical trials defined the maximally tolerated dose (MTD) of eribulin mesylate: NCI-5730, E7389-A001-101, E7389-A001-102 and E7389-J081-105. Eribulin mesylate was given as an intravenous bolus (study NCI) or a one hour infusion (study 101) weekly, every week for three consecutive weeks, of a 28 day schedule in the studies identified as NCI and Study 101. The MTD was defined as 1.4 mg/m^2 in study NCI and 1.0 mg/m^2 in study 101. In study 102, eribulin mesylate was given as a one hour intravenous infusion on day 1, every 21 days and the MTD was defined as 2.0 mg/m^2. Based on the results of the studies identified as NCI and study 101, eribulin mesylate was administered in phase 2 studies at a dose of 1.4 mg/m^2 administered as an intravenous bolus on days 1, 8, and 15 of a 28-day cycle. However, in the initial phase 2 studies, dose delays, omissions, and reductions were frequent because of Grade 3 or 4 neutropenia at the time of the planned day 15 dose. The dose regimen was then modified to 1.4 mg/m^2 administered over 2 min to 10 min on Days 1 and 8 in a 21-day cycle. The recommended phase 2 was then confirmed in the study 105.

Effectiveness in Clinical Trials:
The applicant conducted a phase 2 proof-of-concept clinical trial (E7389-A0001-201) followed by a larger single arm, phase 2 study in advanced breast cancer (E7389-G000-211).

The applicant subsequently conducted study E7389-G000-305, which is an open-label, randomized, parallel, two arm, multicenter controlled phase 3 study in women with locally recurrent breast cancer or metastatic breast cancer, who had previously received two to five prior chemotherapy regimens including an anthracycline and a taxane, at least two of which must have been for advanced disease. Patients must have proven refractory to their most recent chemotherapy regimen, documented by progression on or within six months of therapy. Patients were randomized 2:1 to receive eribulin at a dose of 1.4 mg/m^2 as an intravenous bolus over 2 min to 5 min, on days 1 and 8 of a 21- day course or treatment of physicians' choice (TPC), defined as any single-agent

chemotherapy, hormonal treatment, or biologic therapy approved for the treatment of cancer; or palliative treatment or radiotherapy, administered according to local practice. Patients were stratified by geographic region, human epidermal growth factor receptor 2 status and prior treatment with capecitabine.

The applicant stated that the comparator TPC was used, since there is no clear standard of care after treatment with an anthracycline and a taxane for third and later line in patients with MBC. The choices, in this line of treatment, depend on the prior chemotherapies received, response to previous therapy, tolerability, patient's preference, availability of drugs at the center and the patient's quality of life.

The overall survival, defined as the date of randomization until the date of death due to any cause, was compared between the randomized treatment groups in the intent-to-treat (ITT) population. For patients who did not die (i.e., those who were lost to follow-up or who were alive at the date of data cut-off), the time to death was censored at the time of last contact. Secondary endpoints included progression free survival (PFS), ORR and duration of response (DOR). All available imaging data were subjected to Independent review.

OS was significantly longer with eribulin compared to TPC (p=0.041, Figure 1 from 2.5 Clinical Overview) at a median of 399 days in the eribulin group and 324 days in the TPC group. The applicant stated the results were consistent between the ITT and the per protocol (PP) population.

Figure 1 Kaplan-Meier Analysis of Overall Survival in Study 305 (Intent-To-Treat Population)

Abbreviations: TPC = Treatment of Physician's Choice.
Data source: Study 305 CSR, Figure 2.

The median PFS by Independent Review was numerically longer in the eribulin group, but only reached statistical significance in the PP population, not the ITT population. The ORR was statistically significantly higher in the women who received eribulin (p=0.002). The median DOR was 128 days in the eribulin group, but could not be determined in the TPC group. Only a small number of patients responded in the TPC group.

Effectiveness in Subpopulations of the Registration Trial:
The efficacy of eribulin in different breast cancer subpopulations was evaluated to determine whether there might be factors that affect the efficacy of eribulin. These factors included patient demographic characteristics, breast cancer disease characteristics, prior chemotherapy, and other patient conditions that may affect eribulin exposure or tolerance of eribulin therapy (figures 6 and 7 from module 2.7.3, section 2.7.3.3.6). The ORR in individual subgroups was generally similar to the ORR for the overall population with the largest differences being in subgroups with a small number of patients. Together, these data show that eribulin is effective in breast cancer patients regardless of age, race, geographic region, body size, and ECOG performance status.

Figure 6   Treatment Comparison of Overall Survival by Demographic Characteristics Age, Race and Geographic Region (ITT population: Study 305)

Abbreviations: CI = confidence interval; HR = hazard ratio; TPC = Treatment of Physician's Choice.
(1) N.A./W.E./AU= North America/Western Europe/Australia
Note: Hazard ratio is calculated with TPC as the reference group based on stratified Cox regression adjusted for HER2/*neu* status, prior capecitabine treatment and geographical region as strata.
A smaller hazard ratio is in favor of eribulin. The 95% CI is not presented if it is too wide to fit in the figure.
Data source: Figure 2.3.2.

Figure 7   Treatment Comparison of Overall Survival by Demographic Characteristics Body Size and Baseline ECOG score (ITT population: Study 305)

Abbreviations: CI = confidence interval; BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; TPC = Treatment of Physician's Choice.
Note: Hazard ratio is calculated with TPC as the reference group based on stratified Cox regression adjusted for HER2/*neu* status, prior capecitabine treatment and geographical region as strata.
A smaller hazard ratio is in favor of eribulin. The 95% CI is not presented if it is too wide to fit in the figure.
Data source: Figure 2.3.2.

Safety Evaluation in Clinical Trials:
In the registration trial study 305, almost all patients experienced at least one adverse event (AE), and serious adverse events (SAEs) were reported for approximately one-quarter of patients in both treatment groups. Grade 4 AEs were reported for 29.4% of patients in the eribulin group and 13.4% of patients in the TPC group. Twenty (4.0%) patients and 18 (7.3%) patients had fatal AEs in the eribulin group and the TPC group, respectively.

The most common adverse reactions (incidence $\geq$ 25%) reported in study 305 were asthenia/fatigue, neutropenia, alopecia, nausea, and peripheral neuropathy. Table 2 excerpted from the proposed label lists the non-hematologic toxicity reported in study 305 and table 3 lists the hematologic toxicity reported in study 305.

The applicant summarized the safety data as follows:
- Grade 3-4 treatment-related adverse events were reported in approximately 60% of subjects in the Breast Cancer Population. The incidence of Grade 3-4 events for the most common treatment-related adverse events was low for nausea (1%), febrile neutropenia (5%), peripheral neuropathy (7%), and asthenia/fatigue (8%). The incidence of treatment-related Grade 3-4 neutropenia was 48%. The incidence of treatment-related Grade 3-4 anemia and thrombocytopenia was low (1% for both).
- While the observed hematologic toxicity is relatively frequent and severe, it proved to be manageable with dose delays, dose reductions, and the use of growth factors. Neutropenia occurred in approximately half the Breast Cancer Population treated with eribulin, but led to febrile neutropenia in 4.6% of cases. Neutropenia was the most common cause of treatment delays, reductions, interruptions and discontinuations, with 19% of subjects having treatment delayed, 7% of subjects having a dose reduction, 0.8% of subjects having a dose interruption, and 0.5% of subjects discontinuing treatment for this reason. Febrile neutropenia led to eribulin discontinuation, dose delay, dose interruption and reduction for 0.1%, 0.7%, 0.1% and 2.1% of subjects, respectively.
- Peripheral neuropathy occurred frequently with eribulin (about 1/3 of the subjects in the Breast Cancer Population), although development of severe symptoms (Grade 3 and 4) was reported in <8% of subjects. Subjects were eligible for enrollment with pre-existing neuropathy up to Grade 2. Approximately 5% of the subjects discontinued study therapy due to peripheral neuropathy. Subjects with preexisting neuropathy Grade $\leq$2 and prior history of diabetes did not experience a higher incidence of peripheral neuropathy during treatment with eribulin than subjects without pre-existing peripheral neuropathy.
- Toxicities did not occur more frequently among elderly subjects who received eribulin. Population PK analyses shows eribulin exposure in elderly subjects was similar to that in younger subjects. No specific

dose adjustments are recommended based on age of the subject and the tolerability of eribulin was acceptable in elderly subjects.

- Subjects with ALT or AST >3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, subjects with bilirubin >1.5 x ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia.
- The incidence of severe gastrointestinal toxicity or other toxicities (Grades 3 or 4) was low.
- The incidence of hypersensitivity reactions to eribulin is low, and premedications to prevent hypersensitivity are not required.
- Eribulin is minimally excreted via the kidney. No PK studies were conducted with eribulin in subjects with renal impairment. Based on the population PK analysis, renal impairment is not expected to significantly influence eribulin exposure.
- Of the pooled safety data from Breast Cancer subjects (827 subjects) receiving the proposed dose of eribulin, 39 deaths were reported. Out of these, 6 deaths were reported as possibly or probably treatment-related. The causes of death were most commonly related to disease progression and were not unexpected given the advanced disease of this subject population.
- Treatment-emergent serious adverse events were reported for approximately 27% of the Breast Cancer population.

(b) (4)

Human Pharmacokinetic Data:

The pharmacokinetics of eribulin in humans has been examined after a single dose in 8 phase 1 studies and in 1 phase 2 study. Eribulin doses ranged from 0.125 mg/m^2 to 4.0 mg/m^2 administered as a one hour infusion or an intravenous bolus over 2 min to 10 min.

Summary of Clinical Trials with PK Evaluations			
Study	Regimen	Days	Matrix
101	Days 1, 8 and 15 Every 28 days iv. infusion	Cycle 1, days 1 and 15	Plasma (96 h)
102	Day 1 Every 21 days iv infusion	Cycle 1, day 1	Plasma (96 h) and urine (72 h)
103	Days 1 (and 8) Every 21 days iv bolus	Cycle 1, day 1 ADME (^{14}C-erubulin)	Blood, urine, fecal (8 days)
105	Days 1 and 8 Every 21 days iv bolus	Cycle 1, days 1 and 8	Plasma (168 h) and urine (72 h)
108	Days 1, 8 and 15 Every 28 days iv bolus	Cycle 1, day 1 Hepatic Impairment	Plasma (144 h)
109	Days 1 and 15 iv bolus	Cycle 1, days 1(2) and 15(16) DDI - Ketoconazole	Plasma (144 h)
110	Days 1 and 8 Every 21 days iv bolus	Cycle 1, days 1 and 8 QTc study	Plasma (48 h)
NCI-5730	Days 1, 8, 15 Every 28 days iv bolus	Cycle 1, days 1 and 15	Plasma (72 h) and urine (48 h)
211	Days, 1, 8 and 15 Every 28 days iv bolus	Cycle 1, day 1	Plasma (120 hours) **sparse**

Absorption: The applicant states that the PK of eribulin is characterized by a rapid distribution phase following by a prolonged elimination phase. Eribulin binding to human plasma proteins was relatively low. The plasma protein binding of eribulin (100 ng/mL to 1000 ng/mL) ranged between 49% and 65% in human plasma.

The mean maximal plasma concentration for the proposed dose administered as an intravenous bolus is 186 ± 67.4 ng/mL. Most patients had measurable plasma concentrations of eribulin up to 96 hours after the start of the intravenous infusion in study 101 and 102. The applicant stated that no significant accumulation of eribulin was observed on weekly administration. Eribulin exposure after multiple dosing, following the second or third weekly dose of the first cycle, was comparable to that achieved following a single dose.

Plasma concentrations increased nearly dose proportionally over the dose range in study 101 and 102 with the applicant concluding that exposure was dose-related at doses of 0.25 mg/m^2 to 4.0 mg/m^2.

Distribution: Eribulin has a large volume of distribution at steady state (V$_{ss}$, 43 L/m^2 to114 L/m^2). The eribulin mean blood/plasma concentration ratios time-profile suggests that eribulin demonstrates minimal preferential distribution into the red blood cells.

Metabolism: Eribulin demonstrates low plasma clearance (CL, 1.16 L/h/m^2 to 2.42 L/h/m^2) and metabolism represents a minor component in eribulin clearance. Following administration of 2 mg ^{14}C-eribulin dose to patients, plasma eribulin concentrations were approximately 100% of the total drug derived radioactivity, indicating minimal eribulin metabolism.

CYP3A4 was identified as the major enzyme responsible for eribulin metabolism in human liver microsomes, but CYP-mediated metabolism of eribulin appears to be minor. Several mono-hydroxylated metabolites were found in the *in vitro* hepatic microsomal incubations. A drug interaction study (E7389-E044-109) demonstrated that concomitant administration of ketoconazole, a CYP3A4 inhibitor, had no effect on exposure to eribulin.

Eribulin did not induce CYP1A, CYP3A or CYP2C nor did eribulin alter either the activity or the protein expression of CYP1A or CYP3A (up to 5 μM; 3650 ng/mL), and CYP2C9 or CYP2C19 (up to 10 μM; 7300 ng/mL) in primary cultures of human hepatocytes. No significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 was detected with eribulin concentrations up to 5 μM (3650 ng/mL). Eribulin inhibited CYP3A4 activity with an apparent inhibition constant (K_i) value ranging from 3 μM to 30 μM (2190 ng/mL to 21,900 ng/mL), and the inhibition was demonstrated to be reversible and competitive.

The applicant conducted an *in vitro* study to examine the antiproliferative effects of eribulin mesylate against MDR human cancer cell lines based on overexpression of the P-gp drug efflux pump. P-gp expressing cells were less sensitive to eribulin compared to non P-gp expressing cells. Verapamil markedly increased the potencies of eribulin in P-gp expressing cells.(CAIVT0105; CAIVT0106)

Eribulin reduced P-gp-mediated transport of digoxin in a concentration-dependent manner with an estimated concentration corresponding to half-maximal inhibition (IC_{50}) of >10 μM (7,300 ng/mL). This IC_{50} value represents 10-fold the highest mean C_{max} (700 ng/mL) observed in the phase 1 clinical pharmacology studies. Thus, inhibition of P-gp by eribulin is unlikely to be clinically relevant.

Elimination: The mean plasma concentration vs. time data demonstrated parallel decay curves in the elimination phase for all dose levels in study 101 and 102.

Renal elimination is a minor route for eribulin excretion, with less than 8% of the total clearance of eribulin in the urine from 0 hours to 120 hours. The majority of eribulin is excreted unchanged in feces (mean 71%, 0 hours to 120 hours). Although it cannot be directly measured in patients, biliary excretion may also represent a substantial contribution to eribulin clearance. The mean renal clearance was estimated to be 93 mL/h/m^2 to 372 mL/h/m^2 across dose levels and was 203 mL/h/m^2 for all 21 patients who completed the PK evaluation in study 102.

Hepatic impairment affects the disposition of eribulin by decreasing clearance and prolonging elimination half-life, resulting in increased exposure to eribulin. The applicant proposes that the eribulin dose in patients with moderate hepatic impairment should be reduced to 0.7 mg/m^2.

Sponsor's Population PK Analyses:
A retrospective population pharmacokinetics analysis was performed on data obtained from phase 1 trials and phase 2 trial to assess the influence of weight, age, BSA, gender and creatinine clearance (CLCR) on the pharmacokinetics parameters of eribulin. Population PK analyses showed that eribulin clearance is affected by body weight, serum albumin, alkaline phosphatase and bilirubin. The effects of age, gender, race and concomitant medications (CYP inhibitors and inducers) on clearance were not found to be significant. After normalizing for body weight, there was no effect of creatinine clearance on eribulin clearance

Sponsor's Population PK/PD Analyses:

In the dose-escalation studies, the adverse events (AE) regarded as dose-limiting toxicities (DLT) were neutropenia and fatigue. In the PK/PD analyses of these studies, eribulin exposure was related to neutropenia. The relationship between exposure and fatigue was less consistent across studies. Population exposure/response models were developed to correlate the probability of a subject experiencing grade 4 neutropenia (based on reported AE), grade ≥ 3 fatigue (or asthenia), or grade ≥ 3 neuropathy with post hoc estimates of individual patient exposure derived from the population PK model. The probability of patients experiencing grade ≥ 3 fatigue was found to be independent of eribulin exposure. The probability of patients experiencing grade ≥ 3 neuropathy was related to eribulin exposure and the number of treatment cycles administered, but was low at eribulin exposures that are likely to be experienced in the clinic. The probability of patients experiencing grade 4 neutropenia (based on reported AE) was related to eribulin exposure and plasma AST levels.

A pharmacokinetic/pharmacodynamic (PK/PD) analysis found no relationship between observed eribulin concentration and baseline-adjusted QTc intervals on Days 1 and 8.

Special Populations:
A hepatic impairment study (study 108) in patients with normal hepatic function, mild or moderate hepatic impairment demonstrated that hepatic impairment affects the disposition of eribulin by decreasing clearance and prolonging elimination half-life, resulting in increased exposure to eribulin.

Labeling Statements:
Dosage and Administration

- (b) (4)

Warnings and Precautions

- (b) (4)

Drug Interactions

- (b) (4)

Use in Specific Populations

- (b) (4)

- (b) (4)

Clinical Pharmacology

- (b) (4)

Potential Key Clinical Pharmacology and Pharmacometrics Questions for Scoping Meeting Discussion:
1. Does the exposure-response (ER) relationship for effectiveness support the proposed dose?
2. Does the ER relationship for safety support the proposed dose? Is the proposed dose reduction adequate to reduce the risk of Grade 3/4 neutropenia?
3. Does eribulin prolong the QTc interval?
4. Are the proposed doses for patients with hepatic impairment appropriate?
5. Does renal impairment affect exposure?
6. Are there genomic biomarkers associated with clinical outcomes?
7. Are genetic variants associated with eribulin pharmacokinetics?

Signatures

_____   _____

Stacy S Shord, PharmD   Hong Zhao, PhD

Reviewer   Team Leader

Division of Clinical Pharmacology 5   Division of Clinical Pharmacology 5

Cc: DBOP: RPM – **V Jarral;** MTL – **S Lemery**; MO – **M Donoghue**

      DCP-5: DDD - **B Booth**; DD - **A Rahman**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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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/

STACY S SHORD
08/19/2010

HONG ZHAO
08/19/2010
I concur.

Anshu Marathe
08/19/2010

CHRISTINE E GARNETT
08/19/2010

ISSAM ZINEH
08/19/2010

NAM ATIQUR RAHMAN
08/24/2010

Clinical Pharmacology Review Worksheet

Submission Date: 01-Apr-2010

NDA Number: 201,532
Product Name: eribulin mesylate
Route of Administration: intravenous infusion
Proposed Indication: locally advanced and metastatic breast cancer
Submission Type: NDA-000
Sponsor: Eisai Inc.
Reviewer: Stacy S. Shord, PharmD

Introduction

The Clinical Pharmacology and Biopharmaceutics Filing Form for NDA 201-532 (eribulin mesylate) was finalized on April 30, 2010. This is an addendum to the filing form on behalf of the pharmacometrics review team:

Provide **Appendix IV** of the **Population PK report** which contains the population pharmacokinetics base and final model control streams and output listings.

Recommendations: No action indicated; the information request will be sent to the applicant.

Signatures

Stacy S Shord, Pharm.D.	Hong Zhao, Ph.D.
Reviewer	Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DBOP: RPM – **V Jarral;** MTL –**S Lemery**; MO – **M Donoghue**
       DCP-5: DDD - **B Booth;**   DD - **A Rahman**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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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/

STACY S SHORD
05/03/2010

HONG ZHAO
05/03/2010
I concur.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

NDA Number	201-532	**Brand Name**	Halaven
DCP Division (I, II, III, IV, V)	V	**Generic Name**	Eribulin mesylate
Medical Division	Oncology	**Drug Class**	Halichondrin B Analogue
OCP Reviewer	Stacy S. Shord, PharmD	**Indication(s)**	Locally advanced or metastatic breast cancer who previously received at least two chemotherapy regimens
OCP Team Leader	Hong Zhao, PhD	**Dosage Form**	1 mg per 2 mL intravenous sterile solution
Pharmacometrics Reviewer	Anshu Marathe, PhD	**Dosing Regimen**	1.4 mg/m^2 on days 1 and 8 of each 21-day cycle
Date of Submission	3/30/2010	**Route of Administration**	Slow intravenous bolus over 2 min to 5 min
Estimated Due Date of OCP Review	6/18/2010	**Sponsor**	Eisai Inc.
Medical Division Due Date	9/09/2010	**Priority Classification**	6-month review
PDUFA Due Date	9/30/2010		

Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical comments if any
STUDY TYPE				
Table of contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular listing of all human studies	X			
HPK summary	X			
Labeling	X			
Reference bioanalytical and analytical methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		E7389-E044-103
Isozyme characterization:	X	1		DSD2003-01
Blood/plasma ratio:	X	1		E7389-E044-103
Plasma protein binding:	X	1		DSD2001-38
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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Patients-				
single dose:	X	8		NCI-5730 (dose escalation)
				E7389-A001-101 (dose escalation)
				E7389-A001-102 (dose escalation)
				E7389-J081-105 (RP2D)
				E7389-E044-108 (hepatic impairment)
				E7389-E044-109 (DDI)
				E7389-E044-110 (QTc)
				E7389-G000-211 (supportive study)
multiple dose:	X	4		NCI-5730
				E7389-A001-101
				E7389-J081-105
				E7389-E044-110
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		E7389-E044-109 (ketoconazole)
In-vivo effects of primary drug:				
In-vitro:	X	8		DSD2004-03 (induction CYP1A and CYP3A)
				DDDM2005-03 (inhibition CYP2C)
				DMPK2000-13 (inhibition CYPs)
				DSD2001-31 (inhibition CYP3A)
				DSDM2001-009 (inhibition coadmin. drugs)
				DDDA2008-004 (pgp)
				CAIVT0105 (pgp)
				CAIVT0106 (pgp)
Subpopulation studies -				
ethnicity:	X			popPK
gender:				popPK
geriatrics:	X			popPK
renal impairment:	X			popPK
hepatic impairment:	X	1		E7389-E044-108
pediatrics:				Request waiver
PD:				
Phase 2:	X	2		E7389-A001-201
				E7389-G000-211
Phase 3:	X	1		E7389-G000-305
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3		E7389-A001-101 (ANC, fatigue)
				E7389-A001-102 (ANC, fatigue)
				E7389-E044-110 (QTc)
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	7		Pooled phase 1 (101, 102, 103, 105, 108, 109, 110) and phase 2 data
Data sparse:	X	1		Pooled phase 1 (101, 102, 103, 105, 108, 109, 110) and phase 2 data

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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II. Biopharmaceutics				
Absolute bioavailability:				*Not applicable*
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				*Not applicable*
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
QT$_C$ studies:	X	1		E7389-E044-110
Genotype/phenotype studies	X	4		NCI-5730 (β-tubulin, MAP4, stamin) E7389-E044-103 (CYPs) E7389-E044-108 (CYP3A4) E7389-E044-109 (CYPs)
Chronopharmacokinetics				
Pediatric development plan				Pediatric Waiver Request
Literature references				
Total Number of Studies		11		11 studies conducted in patients

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	All clinical studies completed using eribulin in the same formulation
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Requested waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? <u>Yes</u>

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist	Date

Team Leader/Supervisor	Date

<center>**Clinical Pharmacology - NDA Filing Memo**</center>

NDA:	201-532/000, Original Submission	**IND:** 67,193
Compound:	Eribulin mesylate, 1.0 mg per 2 mL intravenous sterile solution	
Sponsor:	Eisai Inc.	
Filing Date:	May 3, 2010	
Reviewer:	Stacy S. Shord, PharmD	

Background and Mechanism of Action:
Standard therapy for recurrent or metastatic breast cancer (MBC) for last-line therapy, following first- and second-line treatment with appropriate chemotherapy, endocrine therapy and/or biologics, is not defined. First-line therapy provides a response rate (RR) of greater than or equal to 50%, but the cancer typically progresses. Second line therapy typically includes single agent therapy, with capecitabine the most widely used single agent, and it is the only treatment approved for treatment after an anthracycline and a taxane. The overall response rate (ORR) is 20% and the median survival is 10.1 months. Ixabepilone is the only therapy approved for last-line therapy. The ORR is 11.5% and the median survival is 8.6 months.

Eribulin mesylate (E7386) is an analogue of halichondrin B, a natural product isolated from marine sponges (*Halicohondira koadai)* and it is a non-taxane microtubule dynamics inhibitor. Eribulin mesyalte demonstrated a statistically significant and clinically relevant improvement in overall survival (OS) compared to treatment of physicians' choice (TPC) following the completion of a single phase 3 randomized clinical trial. The results of this phase 3 clinical trial are supported by two phase 2 studies in which an ORR of 13.6% (study 201) and 9.3% (study 211) was demonstrated. The proposed indication is 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.

Rationale for Phase 3 Dose Selection:
Four phase 1 dose escalation clinical trials defined the maximally tolerated dose (MTD) of eribulin mesylate: NCI-5730, E7389-A001-101, E7389-A001-102 and E7389-J081-105. Eribulin mesylate was given as an intravenous bolus (study 5730) or a one hour infusion (study 101) weekly, every week for three consecutive weeks, of a 28 day schedule in the studies identified as study 5730 and study 101. The MTD was defined as 1.4 mg/m^2 in study 5730 and 1.0 mg/m^2 in study 101. In study 102, eribulin mesylate was given as a one hour intravenous infusion on day 1, every 21 days and the MTD was defined as 2.0 mg/m^2. Based on the results of the studies identified as study 5730 and study 101, eribulin mesylate was administered in phase 2 studies at a dose of 1.4 mg/m^2 as an intravenous bolus on days 1, 8, and 15 of a 28-day cycle. However, in the initial phase 2 studies, dose delays, omissions, and reductions were frequent because of Grade 3 or 4 neutropenia at the time of the planned day 15 dose. The dose regimen was then modified to 1.4 mg/m^2 as an intravenous bolus on days 1 and 8 of a 21-day cycle. The recommended phase 2 was then confirmed in the study 105.

Effectiveness in Clinical Trials:
The applicant conducted a phase 2 proof-of-concept clinical trial (E7389-A0001-201) followed by a larger single arm, phase 2 study in advanced breast cancer (E7389-G000-211).

The applicant subsequently conducted study E7389-G000-305, which is an open-label, randomized, parallel, two arm, multicenter controlled phase 3 study in women with locally recurrent breast cancer or metastatic breast cancer, who had previously received two to five prior chemotherapy regimens including an anthracycline and a taxane, at least two of which must have been for advanced disease. Patients must have proven refractory to their most recent chemotherapy regimen, documented by progression on or within 6 months of therapy. Patients were randomized 2:1 to receive eribulin at a dose of 1.4 mg/m^2 as an intravenous bolus, on days 1 and

8 of a 21- day course or TPC, defined as any single-agent chemotherapy, hormonal treatment, or biologic therapy approved for the treatment of cancer; or palliative treatment or radiotherapy, administered according to local practice. Patients were stratified by geographic region, human epidermal growth factor receptor 2 (Her-2) status and prior treatment with capecitabine.

The applicant stated that the comparator TPC was used, since there is no clear standard of care after treatment with an anthracycline and a taxane for third and later line in patients with MBC. The choices, in this line of treatment, depend on the prior chemotherapies received, response to previous therapy, tolerability, patient's preference, availability of drugs at the center and the patient's quality of life.

The OS, defined as the date of randomization until the date of death due to any cause, was compared between the randomized treatment groups in the intent-to-treat (ITT) population. For patients who did not die (i.e., those who were lost to follow-up or who were alive at the date of data cut-off), the time to death was censored at the time of last contact. Secondary endpoints included progression free survival (PFS), ORR and duration of response (DR). All available imaging data were subjected to an independent review.

OS was significantly longer with eribulin compared to TPC (p=0.041, Figure 1 from 2.5 Clinical Overview) at a median of 399 days in the eribulin group and 324 days in the TPC group. The applicant stated the results were consistent between the ITT and the per protocol (PP) population.

Figure 1 Kaplan-Meier Analysis of Overall Survival in Study 305 (Intent-To-Treat Population)

Abbreviations: TPC = Treatment of Physician's Choice.
Data source: Study 305 CSR, Figure 2.

The median PFS by Independent Review was numerically longer in the eribulin group, but only reached statistical significance in the PP population, not the ITT population. The ORR was statistically significantly higher in the women who received eribulin (p=0.002). The median DOR was 128 days in the eribulin group, but could not be determined in the TPC group. Only a small number of patients responded in the TPC group.

Effectiveness in Subpopulations of the Registration Trial:
The efficacy of eribulin in different breast cancer subpopulations was evaluated to determine whether there might be factors that affect the efficacy of eribulin. These factors included patient demographic characteristics, breast cancer disease characteristics, prior chemotherapy, and other patient conditions that may affect eribulin exposure or tolerance of eribulin therapy (figures 6 and 7 from module 2.7.3, section 2.7.3.3.6). The ORR in individual subgroups was generally similar to the ORR for the overall population with the largest differences being in subgroups with a small number of patients. Together, these data show that eribulin is effective in breast cancer patients regardless of age, race, geographic region, body size, and ECOG performance status.

Figure 6 Treatment Comparison of Overall Survival by Demographic Characteristics Age, Race and Geographic Region (ITT population: Study 305)

Abbreviations: CI = confidence interval; HR = hazard ratio; TPC = Treatment of Physician's Choice.
(1) N.A./W.E./AU= North America/Western Europe/Australia
Note: Hazard ratio is calculated with TPC as the reference group based on stratified Cox regression adjusted for HER2/neu status, prior capecitabine treatment and geographical region as strata.
A smaller hazard ratio is in favor of eribulin. The 95% CI is not presented if it is too wide to fit in the figure.
Data source: Figure 2.3.2.

Figure 7 Treatment Comparison of Overall Survival by Demographic Characteristics Body Size and Baseline ECOG score (ITT population: Study 305)

Abbreviations: CI = confidence interval; BSA = body surface area; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; TPC = Treatment of Physician's Choice.
Note: Hazard ratio is calculated with TPC as the reference group based on stratified Cox regression adjusted for HER2/neu status, prior capecitabine treatment and geographical region as strata.
A smaller hazard ratio is in favor of eribulin. The 95% CI is not presented if it is too wide to fit in the figure.
Data source: Figure 2.3.2.

Safety Evaluation in Clinical Trials:

In the registration trial study 305, the most common adverse reactions (incidence ≥ 25%) reported in study 305 were asthenia/fatigue, neutropenia, alopecia, nausea, and peripheral neuropathy. Table 2 excerpted from the proposed label lists the non-hematologic toxicity reported in study 305 and table 3 lists the hematologic toxicity reported in study 305.

The applicant summarized the safety data as follows:

- Grade 3-4 treatment-related adverse events were reported in ~ 60% of subjects in the Breast Cancer Population. The incidence of Grade 3-4 events for the most common treatment-related adverse events was low for nausea (1%), febrile neutropenia (5%), peripheral neuropathy (7%), and asthenia/fatigue (8%). The incidence of treatment-related Grade 3-4 neutropenia was 48%. The incidence of treatment-related Grade 3-4 anemia and thrombocytopenia was low (1% for both).
- While the observed hematologic toxicity is relatively frequent and severe, it proved to be manageable with dose delays, dose reductions, and the use of growth factors. Neutropenia occurred in approximately half the Breast Cancer Population treated with eribulin, but led to febrile neutropenia in 4.6% of cases. Neutropenia was the most common cause of treatment delays, reductions, interruptions and discontinuations, with 19% of subjects having treatment delayed, 7% of subjects having a dose reduction, 0.8% of subjects having a dose interruption, and 0.5% of subjects discontinuing treatment for this reason. Febrile neutropenia led to eribulin discontinuation, dose delay, dose interruption and reduction for 0.1%, 0.7%, 0.1% and 2.1% of subjects, respectively.
- Peripheral neuropathy occurred frequently with eribulin (about 1/3 of the subjects in the Breast Cancer Population), although development of severe symptoms (Grade 3 and 4) was reported in <8% of subjects. Subjects were eligible for enrollment with pre-existing neuropathy up to Grade 2. Approximately 5% of the subjects discontinued study therapy due to peripheral neuropathy. Subjects with preexisting neuropathy Grade ≤2 and prior history of diabetes did not experience a higher incidence of peripheral neuropathy during treatment with eribulin than subjects without pre-existing peripheral neuropathy.
- Toxicities did not occur more frequently among elderly subjects who received eribulin. Population PK analyses shows eribulin exposure in elderly subjects was similar to that in younger subjects.
- Subjects with ALT or AST >3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, subjects with bilirubin >1.5 x ULN also had a higher incidence of Grade 4 neutropenia and febrile neutropenia.

- Based on the population PK analysis, renal impairment is not expected to significantly influence eribulin exposure.
- Of the pooled safety data from Breast Cancer subjects (827 subjects) receiving the proposed dose of eribulin, 39 deaths were reported. Out of these, 6 deaths were reported as possibly or probably treatment-related. The causes of death were most commonly related to disease progression and were not unexpected given the advanced disease of this subject population.
- Treatment-emergent serious adverse events were reported for approximately 27% of the Breast Cancer population.

(b) (4)

Human Pharmacokinetic Data:
The pharmacokinetics of eribulin in humans has been examined in 8 phase 1 studies and in one phase 2 study. Eribulin doses ranged from 0.125 mg/m^2 to 4.0 mg/m^2 administered as a one hour infusion or an intravenous bolus.

Summary of Clinical Trials with PK Evaluations			
Study	Regimen	Days	Matrix
101	Days 1, 8 and 15 Every 28 days iv. infusion	Cycle 1, days 1 and 15	Plasma (96 h)
102	Day 1 Every 21 days iv infusion	Cycle 1, day 1	Plasma (96 h) and urine (72 h)
103	Days 1 (and 8) Every 21 days iv bolus	Cycle 1, day 1 ADME (^{14}C-erubulin)	Blood, urine, fecal (8 days)
105	Days 1 and 8 Every 21 days iv bolus	Cycle 1, days 1 and 8	Plasma (168 h) and urine (72 h)
108	Days 1, 8 and 15 Every 28 days iv bolus	Cycle 1, day 1 Hepatic Impairment	Plasma (144 h)
109	Days 1 and 15 iv bolus	Cycle 1, days 1(2) and 15(16) DDI - Ketoconazole	Plasma (144 h)
110	Days 1 and 8 Every 21 days iv bolus	Cycle 1, days 1 and 8 QTc study	Plasma (48 h)
NCI-5730	Days 1, 8, 15 Every 28 days iv bolus	Cycle 1, days 1 and 15	Plasma (72 h) and urine (48 h)
211	Days, 1, 8 and 15 Every 28 days iv bolus	Cycle 1, day 1	Plasma (120 hours) **sparse**

Absorption: The applicant states that the PK of eribulin is characterized by a rapid distribution phase following by a prolonged elimination phase. Eribulin binding to human plasma proteins was relatively low. The plasma protein binding of eribulin (100 ng/mL to 1000 ng/mL) ranged between 49% and 65% in human plasma.

The mean maximal plasma concentration (C_{max}) for the proposed dose administered as an intravenous bolus is 186 ± 67.4 ng/mL. Most patients had measurable plasma concentrations of eribulin up to 96 hr after the start of the intravenous infusion in study 101 and 102. The applicant stated that no significant accumulation of eribulin was observed on weekly administration. Eribulin exposure after multiple dosing, following the second or third weekly dose of the first cycle, was comparable to that achieved following a single dose.

Plasma concentrations increased nearly dose proportionally over the dose range in study 101 and 102 with the applicant concluding that exposure was dose-related at doses of 0.25 mg/m^2 to 4.0 mg/m^2.

Distribution: Eribulin has a large volume of distribution at steady state (V$_{ss}$, 43 L/m^2 to114 L/m^2). The eribulin mean blood/plasma concentration ratios time-profile suggests that eribulin demonstrates minimal preferential distribution into the red blood cells.

<u>Metabolism</u>: Eribulin demonstrates low plasma clearance (CL, 1.16 L/h/m^2 to 2.42 L/h/m^2) and metabolism represents a minor component in eribulin clearance. Following administration of 2 mg ^{14}C-eribulin dose to patients, plasma eribulin concentrations were approximately 100% of the total drug derived radioactivity, indicating minimal eribulin metabolism.

CYP3A4 was identified as the major enzyme responsible for eribulin metabolism in human liver microsomes, but CYP-mediated metabolism of eribulin appears to be minor. Several mono-hydroxylated metabolites were found in the *in vitro* hepatic microsomal incubations. A drug interaction study (E7389-E044-109) demonstrated that concomitant administration of ketoconazole, a CYP3A4 inhibitor, had no effect on exposure to eribulin.

Eribulin did not induce CYP1A, CYP3A or CYP2C nor did eribulin alter either the activity or the protein expression of CYP1A or CYP3A (up to 5 μM; 3650 ng/mL), and CYP2C9 or CYP2C19 (up to 10 μM; 7300 ng/mL) in primary cultures of human hepatocytes. No significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 was detected with eribulin concentrations up to 5 μM (3650 ng/mL). Eribulin inhibited CYP3A4 activity with an apparent inhibition constant (K_i) value ranging from 3 μM to 30 μM (2190 ng/mL to 21,900 ng/mL), and the inhibition was demonstrated to be reversible and competitive.

The applicant conducted an *in vitro* study to examine the antiproliferative effects of eribulin mesylate against multi-drug resistant (MDR) human cancer cell lines based on overexpression of the P-glycoprotein (P-gp) drug efflux pump. P-gp expressing cells were less sensitive to eribulin compared to non P-gp expressing cells. Verapamil markedly increased the potencies of eribulin in P-gp expressing cells.(CAIVT0105; CAIVT0106)

Eribulin reduced P-gp-mediated transport of digoxin in a concentration-dependent manner with an estimated concentration corresponding to half-maximal inhibition (IC_{50}) of >10 μM (7,300 ng/mL). This IC_{50} value represents 10-fold the highest mean C_{max} (700 ng/mL) observed in the phase 1 clinical pharmacology studies. Thus, inhibition of P-gp by eribulin is unlikely to be clinically relevant.

<u>Elimination</u>: The mean plasma concentration vs. time data demonstrated parallel decay curves in the elimination phase for all dose levels in study 101 and 102.

Renal elimination is a minor route for eribulin excretion, with less than 8% of the total clearance of eribulin in the urine from 0 hours to 120 hours. The majority of eribulin is excreted unchanged in feces (mean 71%, 0 hr to 120 hr). Although it cannot be directly measured in patients, biliary excretion may also represent a substantial contribution to eribulin clearance. The mean renal clearance was estimated to be 93 mL/h/m^2 to 372 mL/h/m^2 across dose levels and was 203 mL/h/m^2 for all 21 patients who completed the PK evaluation in study 102.

Hepatic impairment affects the disposition of eribulin by decreasing clearance and prolonging elimination half-life, resulting in increased exposure to eribulin. The applicant proposes that the eribulin dose in patients with moderate hepatic impairment should be reduced to 0.7 mg/m^2.

Sponsor's Population PK Analyses:
A retrospective population pharmacokinetics analysis was performed on data obtained from phase 1 trials and phase 2 trial to assess the influence of weight, age, BSA, gender and creatinine clearance (CLCR) on the pharmacokinetics parameters of eribulin. Population PK analyses showed that eribulin clearance is affected by body weight, serum albumin, alkaline phosphatase and bilirubin. The effects of age, gender, race and concomitant medications (CYP inhibitors and inducers) on clearance were not found to be significant. After normalizing for body weight, there was no effect of creatinine clearance on eribulin clearance
Sponsor's Population PK/PD Analyses:

In the dose-escalation studies, the adverse events (AE) regarded as dose-limiting toxicities (DLT) were neutropenia and fatigue. In the PK/PD analyses of these studies, eribulin exposure was related to neutropenia. The relationship between exposure and fatigue was less consistent across studies. Population exposure/response models were developed to correlate the probability of a subject experiencing grade 4 neutropenia, grade ≥ 3 fatigue (or asthenia), or grade ≥ 3 neuropathy with post hoc estimates of individual patient exposure derived from the population PK model. The probability of patients experiencing grade ≥ 3 fatigue was found to be independent of eribulin exposure. The probability of patients experiencing grade ≥ 3 neuropathy was related to eribulin exposure and the number of treatment cycles administered, but was low at eribulin exposures that are likely to be experienced in the clinic. The probability of patients experiencing grade 4 neutropenia (based on reported AE) was related to eribulin exposure and plasma AST levels.

A pharmacokinetic/pharmacodynamic analysis found no relationship between observed eribulin concentration and baseline-adjusted QTc intervals on Days 1 and 8.

Special Populations:
A hepatic impairment study (study 108) in patients with normal hepatic function, mild or moderate hepatic impairment demonstrated that hepatic impairment affects the disposition of eribulin by decreasing clearance and prolonging elimination half-life, resulting in increased exposure to eribulin.

Labeling Statements:
Dosage and Administration
- (b) (4)

Warnings and Precautions
- (b) (4)

Drug Interactions
- (b) (4)

Use in Specific Populations
- (b) (4)

- (b) (4)

Clinical Pharmacology

- (b) (4)

Potential Key Clinical Pharmacology and Pharmacometrics Questions for Scoping Meeting Discussion:

1. Is the 1.4 mg/m^2 dose optimum based on the exposure/response relationship?
2. Are the proposed dose reductions to a dose of 1.1 mg/m^2 and then to 0.7 mg/m^2 based on hematological toxicity appropriate? (effectiveness)
3. Are the proposed dose reductions to a dose of 1.1 mg/m^2 and then to 0.7 mg/m^2 based on non-hematological grade 3-4 toxicity appropriate? (effectiveness)
4. Are the proposed dose adjustments based on hepatic impairment (decrease dose 50%) appropriate?

Signatures

Stacy S Shord, PharmD	Hong Zhao, PhD
Reviewer	Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DBOP: RPM – **V Jarral;** MTL – **S Lemery**; MO – **M Donoghue**
        DCP-5: DDD - **B Booth**; DD - **A Rahman**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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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/

STACY S SHORD
04/29/2010

HONG ZHAO
04/29/2010
I concur.

Clinical Pharmacology Review

NDA	201-532
Submission Date:	March 30, 2010
Brand Name:	HALAVEN^{TM}
Generic Name:	Eribulin mesylate for injection
Formulation/Strength:	1.0 mg eribulin mesylate in a single-use vial
OCP Reviewer:	Stacy S. Shord, Pharm.D.
OCP Team Leader:	Hong Zhao, Ph.D.
Pharmacometrics Reviewer:	Anshu Marathe, Ph.D.
Pharmacometrics Team Leader:	Christine Garnett, Pharm.D.
Genomics Team Leader:	Issam Zineh, Pharm.D., MPH
OCP Division:	Division of Clinical Pharmacology 5
OND Division:	Division of Biological Oncology Products
Applicant:	Eisai Inc.
Submission Type; Code:	Original NDA; 000
Dosing regimen:	1.4 mg/m^2 administered intravenously (IV) over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.
Indication:	Patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane for locally advanced or metastatic breast cancer.

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1 EXECUTIVE SUMMARY

Eribulin (eribulin mesylate or E7389) is a new molecular entity that inhibits microtubule growth leading to nonproductive tubulin aggregates. The proposed indication is for the third-line treatment of patients with locally advanced or metastatic breast cancer.

Dose Selection and Pharmacokinetics: The proposed dosing regimen is 1.4 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. Dense pharmacokinetic (PK) samples are available from 125 patients enrolled into eight trials and sparse PK samples are available from 211 patients enrolled into a single phase 2 trial. Eribulin is a substrate and weak inhibitor of P-glycoprotein. It is eliminated primarily unchanged in the feces (72% of the dose). Increased systemic exposure to eribulin is demonstrated in patients with mild and moderate hepatic impairment; a lower initial starting dose is recommended for patients with mild and moderate hepatic impairment (1.1 mg/m^2 and 0.7 mg/m^2, respectively). Although only 9% of the dose is renally eliminated, moderate renal impairment increased the mean geometric systemic exposure by 2-fold based on the available data. A lower initial starting dose (1.1 mg/m^2) is recommended for patients with moderate renal impairment. We recommend a post-marketing requirement to assess the effect of severe renal impairment on pharmacokinetics of eribulin.

Efficacy and Safety: Eribulin demonstrated a statistically significant improvement in overall survival by 75 days (median: 399 days) compared to the treatment of physicians' choice (median: 324 days) following the completion of a single registration trial (E7389-G000-305). The results of this trial are supported by two single-arm phase 2 trials (E7389-A0001-201 and E7389-G000-211). The dose-limiting toxicities observed were neutropenia, febrile neutropenia and fatigue. The maximum mean QTcF change from baseline is 11 msec with an upper bound of the 2-sided 90% confidence interval of 18 msec observed on Day 8 of the dosing cycle, suggesting a delayed effect of eribulin on QTc interval prolongation.

Exposure-Response: A conclusive exposure-response (E-R)relationship could not be established for clinical efficacy endpoints including overall survival (OS) and objective response rate (ORR) possibly due to limited exposure data that was collected as sparse PK samples (N=211) at only one dose level (1.4 mg/m^2) in a single phase 2 trial. An E-R relationship for grade 3/4 neutropenia suggests that a dose reduction from 1.4 mg/m^2 to 1.1 mg/m^2 will reduce the risk of grade 3/4 neutropenia by 3%. Further dose reduction to 0.7 mg/m^2 will reduce the risk by 7%. In the registration trial, 23% of the patients in the eribulin arm required dose delays or dose reductions or discontinued treatment due to neutropenia. Eighteen percent (18%) of the patients in the treatment arm received G-CSF. In the registration trial, neutropenia was managed reasonably well with dose delays, dose reductions, discontinuations and G-CSF.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed NDA 201-532 and found the clinical pharmacology data submitted in this NDA acceptable.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

We recommend the following phase 4 requirement. The additional comments should be conveyed to the applicant for further consideration.

1.2.1 Post Marketing Requirements

- Conduct a clinical trial to assess the effect of severe renal impairment on the pharmacokinetics of eribulin.

1.2.2 Additional Comments for the Applicant's Consideration

We also recommend the applicant to:
- Collect sparse pharmacokinetic data from all subjects in future development programs. The purpose is to develop exposure response relationship for efficacy and safety endpoints to support proposed dosing recommendations and dose adjustments.
- Characterize the predictive and/or prognostic relationship between β-tubulin, microtubule associated proteins, and Pgp mRNA expression in tumors within ongoing and future randomized, controlled trials.
- Collect germline DNA to enable future pharmacogenetic analyses of eribulin response and tolerability (e.g. neuropathy) in ongoing and future clinical trials.
- Determine *in vitro* whether eribulin is a substrate and an inhibitor of BCRP, OATP1B1 and OATP1B3.
- Explore mechanisms for the delayed effect on the QTc interval by performing a hERG trafficking study for parent and relevant metabolites with concurrent positive control like arsenic trioxide and pentamidine in further non-clinical testing.
- Explore the delayed effect on the QTc interval by performing a study to detect delay in distribution to myocardium in further non-clinical testing.

Signatures:

Stacy S Shord, Pharm.D.	Hong Zhao, Ph.D.
Reviewer	Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Anshu Marathe, Ph.D.	Christine Garnett, Pharm.D.
Pharmacometrics Reviewer	Pharmacometrics Team Leader
Division of Pharmacometrics	Division of Pharmacometrics

Nam Atiqur Rahman, Ph.D.	Issam Zineh, Pharm.D., M.P.H.
Director	Associate Director for Genomics
Division of Clinical Pharmacology 5	Genomics Group

Cc: DBOP: RPM-**V Jarral**; MTL-**S Lemery**; MO-**M Donoghue**

      DCP-5:   DDD - **B Booth**

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Mechanism of Action: Eribulin (eribulin mesylate, E7389) is a synthetic halichondrin B analog, a natural product isolated from the marine sponge *Halichondrin okadai.* It is a microtubule inhibitor that blocks the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates.

Efficacy and Safety: The proposed indication is for the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapy regimens for advanced disease. The proposed dosing regimen is 1.4 mg/m^2 of eribulin mesylate administered as an intravenous bolus over 2 to 5 min on Days 1 and 8 of a 21-day cycle. In a single phase 3 randomized clinical trial (E7389-G000-305), treatment with eribulin showed a statistically significant improvement in overall survival (OS) compared to treatment of physicians' choice (TPC) (median 399 days vs. 324 days, p=0.041). The results of this trial are supported by two single-arm phase 2 trials in which an overall response rate (ORR) of 13.6% (E7389-A0001-201) and 9.3% (E7389-G000-211) was demonstrated.

Exposure-Response: Pharmacokinetic (PK) data was not collected in the phase 3 trial and an exposure-response (E-R) analysis was conducted using the sparse PK samples collected from a single phase 2 trial (E7389-G000-211) in 211 patients who received the proposed clinical dose of 1.4 mg/m^2. A conclusive E-R relationship could not be identified for OS, progression free survival (PFS) and ORR possibly due to the sparse PK samples collected at only one dose level in this single phase 2 trial.

The dose-limiting toxicities observed were neutropenia, febrile neutropenia and fatigue. The E-R relationship for grade 3/4 neutropenia suggests that a dose reduction from 1.4 mg/m^2 to 1.1 mg/m^2 will reduce the risk of grade 3/4 neutropenia by 3 %. A dose reduction of 50% to 0.7 mg/m^2 will reduce the risk by 7%. In the registration trial, 23% of the patients in the eribulin arm experienced a dose delay or dose reduction or discontinued treatment due to neutropenia. Eighteen percent (18%) of the patients in the eribulin arm received G-CSF. Neutropenia was managed reasonably well with dose delays, dose reductions, discontinuations and G-CSF. Patients with elevated levels of aspartate transaminase (AST) had higher sensitivity to neutropenia at the same exposures. A shallow E-R relationship was observed for febrile neutropenia.

A delayed non-concentration dependent prolongation of QTc interval was observed in the dedicated QT trial (E7389-E044-110). The largest upper bound of the 2-sided 90% confidence interval (CI) for the change from baseline in QTcF was 18 ms on Day 8. We recommend further non-clinical testing to assess eribulin's effect on hERG trafficking and biodistribution to the myocardium.

Dose Selection and Pharmacokinetics: The dosing regimen selection was based on two dose escalation clinical trials that defined the maximally tolerated dose (MTD) of eribulin. The applicant collected dense PK samples from 125 patients in eight clinical trials and sparse PK samples in 211 patients in a single phase 2 trial. The PK profile of eribulin is characterized by a rapid distribution phase. Eribulin's binding to human plasma proteins ranges between 49% and 65%. The area under the concentration vs. time curve (AUC$_{0\text{-inf}}$) linearly increased at doses of 0.25 mg/m^2 to 4 mg/m^2. No accumulation of eribulin was observed on weekly administration as

similar exposure was observed following administration of an intravenous bolus on Days 1 and 8 of cycle 1 in patients enrolled into study 105. The geometric mean terminal phase half-life was 37 hours to 43 hours in the dose escalation trials.

The major elimination pathway in humans is fecal (82% of dose; 88% as eribulin). Renal elimination (< 9%) and metabolism represents a minor contribution. *In vitro,* CYP3A4 is responsible for eribulin negligible hepatic metabolism (<1%). A drug-drug interaction trial (E7389-E044-109) showed that the geometric mean dose-normalized eribulin exposure (AUC) is similar when administered in combination with ketoconazole, a strong CYP3A4 inhibitor.

Specific Populations: Reduced eribulin clearance is demonstrated in patients with mild and moderate hepatic impairment by 1.7- and 2.3-fold, respectively; a lower starting dose is recommended for patients with mild (1.1 mg/m^2) and moderate (0.7 mg/m^2) hepatic impairment. The safety of eribulin in patients with severe hepatic impairment is unknown and these patients should not receive eribulin.

The population PK analysis shows a trend between creatinine clearance and eribulin clearance for patients with moderate renal impairment. Based on non-compartmental analysis of dense PK samples, moderate renal impairment increased eribulin exposure (the geometric mean dose-normalized AUC) by 2-fold. A lower starting dose (1.1 mg/m^2) is recommended for patients with moderate renal impairment. The safety of eribulin in patients with severe renal impairment is unknown and we recommend a clinical trial to assess the effect of severe renal impairment on the PK of eribulin.

The population PK analysis shows no clinically meaningful effect of age, gender and race on the PK of eribulin. The concomitant use of CYP3A4 inducers and inhibitors does not affect the PK of eribulin. However, these data should be interpreted cautiously because information regarding the dose and time of administration of these concomitant medications is unavailable.

Eribulin does not inhibit or induce CYP1A or CYP2C isozymes. It does demonstrate reversible and competitive inhibition of CYP3A4 with an apparent inhibition constant (K_i) value ranging from 3 μM to 30 μM (2.2 μg/mL to 22 μg/mL). The probability of a clinically relevant drug-drug interaction of eribulin with CYP3A4 in humans is remote based on the ratio of the mean maximal plasma concentration reported following an intravenous bolus at the proposed clinical dose to the K_i value. Eribulin is a substrate of P-glycoprotein (Pgp) and weak inhibitor of Pgp.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Eribulin (eribulin mesylate, E7389) is a synthetic halichondrin B analog, a natural product isolated from the marine sponge *Halichondrin okadai.* The drug product is a sterile, ready-to-use, clear, colorless aqueous solution for intravenous administration with 1 mg of eribulin mesylate in a 2 mL fill volume per vial.

Physical-chemical Properties

1. Structural formula:
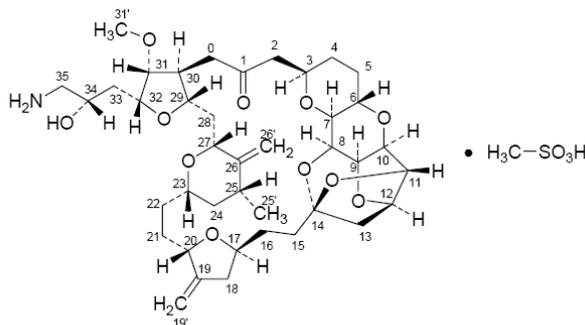
2. Established name: eribulin mesylate, E7389

3. Molecular Weight: 826.0 g/mol (729.9 g/mol for free base)

4. Molecular Formula: C40H59NO11

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

6. Solubility: Freely soluble in water, methanol, ethanol, 1-octanol, benzyl alcohol, dichloromethane, dimethylsulfoxide, *N*-methylpyrrolidone and ethyl acetate; soluble in acetone; sparingly soluble in acetonitrile; practically insoluble in *tert*-butyl methyl ether, *n*-heptane and *n*-pentane.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Eribulin is a microtubule inhibitor that blocks the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates. Eribulin leads to G_2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

The proposed indication is the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapy regimens, including an anthracycline and a taxane, for advanced disease.

2.1.3 What are the proposed dosage and route of administration?

The proposed dosage and route of administration are 1.4 mg/m^2 as an intravenous bolus over 2 to 5 min on Days 1 and 8 of a 21-day cycle until disease progression or intolerance. In the registration trial, the patients received eribulin at a median of 5 cycles or a median duration of 118 days.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical Pharmacology Trials: The applicant conducted three dose escalation clinical trials, six additional clinical trials (**Table 1**) and 12 *in vitro* studies (see **Table 8**) using human biomaterials, to support the clinical pharmacology evaluation of eribulin. A manuscript describing a phase 1 dose-escalation clinical trial conducted by the National Cancer Institute (NCI) is also included. Multiple pharmacokinetic (PK) analyses were conducted to identify patient factors that may affect the PK parameters. Models were developed to explore the link between exposure and the probability of adverse events of grade 3 or higher, and the possible relationships between eribulin exposure and measures of clinical outcome. The population PK analysis includes data collected from a total of 336 patients. PK/PD (pharmacodynamic) and PK/AE (adverse event) analyses were conducted in women with breast cancer with data from a single phase 2 clinical trial; additional PK/AE analyses were completed as part of the three dose escalation trials. The expression of biomarkers associated with resistance to tubulin binding agents was measured as part of study NCI-5730 and study 201.

Phase 2 Trials: The applicant initially conducted a single-arm phase 2 proof-of-concept clinical trial (E7389-A0001-201) and collected tumor biomarkers. A larger single-arm, phase 2 trial in advanced breast cancer (E7389-G000-211) followed and sparse PK samples were collected.

Phase 3 Trial: The registration trial E7389-G000-305 was an open-label, randomized, parallel, two arm, multicenter controlled phase 3 trial conducted in women with locally recurrent or metastatic breast cancer, who had previously received two to five prior chemotherapy regimens, including an anthracycline and a taxane, at least two of which must have been for advanced disease. The primary objective was to compare the overall survival (OS) of patients treated with eribulin vs. TPC (treatment of physician's choice). TPC was defined as any single-agent chemotherapy, hormonal treatment, or biologic therapy approved for the treatment of cancer; or palliative treatment or radiotherapy, administered according to local practice. The secondary objectives were to compare progression free survival (PFS) between the two treatment groups and measure the ORR and duration of response in each treatment group. Patients must have proven refractory to their most recent chemotherapy regimen, documented by progression on or within 6 months of therapy. Patients were randomized 2:1 to receive eribulin at a dose of 1.4 mg/m^2 as an intravenous bolus, on Days 1 and 8 of a 21- day course or TPC. Patients were stratified by geographic region, human epidermal growth factor receptor 2 (Her-2) status and prior treatment with capecitabine.

Table 1. Summary of clinical pharmacology trials				
Study Number	**Objectives**	**Design**	**Subject Number** [a]	**Treatment**
NCI-5730	To determine the MTD, describe the toxicities of eribulin, evaluate the PK of eribulin, determine the in vivo anti-mitotic activity of eribulin and document clinical responses to eribulin.	Open-label, non-randomized, dose titration trial	40/29	0.125 to 2 mg/m^2 as an IV bolus over 1-2 minutes Days 1, 8 and 15, every 28 days
101	To determine PK of eribulin in patients with advanced solid tumors.	Open-label, non-randomized, multicenter, dose-finding trial	33/32	0.25 to 1.4 mg/m^2 as a one-hour IV infusion Days 1, 8 and 15, every 28 days
102	To determine PK of eribulin in patients with advanced solid tumors.	Open-label, non-randomized, multicenter, dose-finding trial	21/21	0.25 to 4.0 mg/m^2 as a one-hour IV infusion on Day 1, every 21 days
103	To determine the excretion balance and elucidate the metabolic pathway of eribulin in vivo after a single dose of ^{14}C- eribulin in patients with advanced solid tumors.	Open-label, single center, single arm trial	6/6	^{14}C-E7389 acetate 2 mg as an intravenous infusion on Day 1 of Cycle 1
105	To determine the DLT of eribulin and estimate the MTD in patients with solid tumors. In addition, preliminary efficacy, safety and tolerability and PK were evaluated.	A stepwise dose-ascending, single center, non-randomized, open-label trial	15/15	0.7, 1, 1.4 or 2 mg/m^2 as an IV bolus over 2-10 minutes on Days 1 and 8, every 21 days
108	To study the effects of hepatic impairment on plasma PK parameters of eribulin and explore safety and tolerability in patients with reduced hepatic function.	Open-label, multi-center, single arm trial	17/17	Normal hepatic function: 1.4mg/m^2 Mild impairment: 1.1mg/m^2 Moderate impairment: 0.7mg/m^2 as an IV bolus over 2-5 minutes on Days 1 and 8, every 21 days
109	To study the influence of repeated oral administration of ketoconazole on the plasma PK of eribulin.	Open-label, non-randomized, single-center trial	12/10	Eribulin Group 1: 1.4 mg/m^2 on Day 1 and 0.7 mg/m^2 on Day 15 in Cycle 1. Group 2: 0.7 mg/m^2 on Day 1 and 1.4 mg/m^2 on Day 15 of Cycle 1. Ketoconazole Group 1: 200 mg on Days 15 and 16 of Cycle 1 Group 2: 200 mg on Days 1 and 2 of Cycle 1

Study Number	Primary Objective	Design	Subject Number [a]	Treatment
110	To assess whether eribulin has an impact on the ECG with focus on cardiac repolarization.	Open-label, multi-center, single arm trial	26/26	1.4 mg/m^2 as an IV bolus over 2-5 minutes on Days 1 and 8, every 21 days
201	To determine the efficacy, quality of life, pharmacogenetics, safety and tolerability of eribulin in patients with advanced/ metastatic breast cancer.	Open-label, single-arm, multi-center trial	104/26	1.4mg/m^2 as a 5 minute IV bolus weekly, Days 1, 8 and 15, every 28 days or Days 1 and 8, every 21 days
211	To evaluate the efficacy, safety and PK-PD of eribulin in patients with locally advanced or metastatic breast cancer.	Open-label, single-arm, multicenter trial	299/211	1.4mg/m^2 as an IV bolus over 2-5 minutes on Days 1 and 8, every 21 days

[a] enrolled / included in PK or genomic analysis

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The applicant conducted two phase 2 and one phase 3 clinical trials. **Table 2** summarizes the response endpoints and biomarkers evaluated in each of these trials.

Table 2. Summary of response endpoints or biomarkers in clinical trials			
Study Number	Primary Objective	Primary Endpoint	Secondary Endpoints
201	To determine the response rate to eribulin monotherapy in patients with advanced/metastatic breast cancer.	ORR	Adverse events Duration of response Time to progression OS Vital signs ECG evaluations Quality of life Performance status Pain Tumor biomarkers
211	To evaluate the efficacy and safety of eribulin in patients with locally advanced or metastatic breast cancer.	ORR	Duration of response OS PFS Adverse events Vital signs ECG evaluations Quality of life Performance status Pain Population PK/PD analysis
305	To compare the overall survival of patients treated with eribulin vs. TPC in patients with locally recurrent or metastatic breast cancer.	OS	PFS Response rate Duration of response Adverse events Vital signs ECG evaluations Performance status

Phase 2 Clinical Trials: Sparse PK samples were collected from 211 patients enrolled into study 211, which provided data for exploration of an E-R relationship for effectiveness and safety. Tumor expression of β-tubulin and other microtubule related proteins were measured in samples collected from 26 patients enrolled into study 201. These biomarkers are associated with tumor aggressiveness and resistance to tubulin binding agents (Kavallaris M. Nat Rev Cancer 2010). These biomarkers were also evaluated in a limited number of patients enrolled in the dose escalation trial NCI-5730.

Phase 3 Registration Trial: OS was defined as the date of randomization until the date of death due to any cause, between the randomized treatment groups in the intent-to-treat (ITT) population. For patients who did not die (i.e., those who were lost to follow-up or who were alive at the date of data cut-off), the time to death was censored at the time of last contact.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Eribulin is the major circulating moiety and it was measured in plasma and urine samples collected during clinical trials using one of three validated LC-MS/MS (high performance liquid chromatography tandem mass spectrometry) methods. Eribulin accounted for 91% of the total radioactivity in the urine and 88% of the total radioactivity in the feces. It undergoes limited metabolism (<1%) by CYP3A4 to several mono-hydroxylated metabolites (DDS-2003-001).

See Section 2.6 for analytical methodologies.

2.2.4 Exposure-response

A conclusive E-R relationship for ORR, OS and PFS could not be established for eribulin due to limited exposure data available by our Pharmacometrics group.

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

An exploratory exposure-efficacy analysis was conducted using data from study 211, because PK samples were not collected in the registration trial (study 305). In study 211, sparse PK samples were collected from 211 patients at four of the following time points that were selected by randomization upon enrollment: 5-10, 15-30, 30-60, and 60-90 minutes; and 2-4, 4-8, 10-24, 48, 72, and 96-120 hours after the start of the infusion of the first eribulin dose (1.4 mg/m^2) during cycle one. The ORR by AUC quartile with 95% confidence intervals (CI) is shown in **Figure 1.** Given the CI, there appears to be no visual relationship between AUC and the ORR. A time-to-event analysis was performed to assess the E-R relationship for effectiveness based on PFS and OS. The PFS and OS curves of patients in different AUC-quartile groups overlapped, thus indicating a lack of an E-R relationship (**Figure 1**). A likely reason for not observing an E-R relationship is that this was a single arm trial with only one dose level that did not result in a wide range of exposures.

Figure 1. Exposure-response relationship for eribulin mesylate in 211 patients enrolled into a single phase 2 clinical trial following doses of 1.4 mg/m^2

Panel A Overall response rate	Panel B Progression free survival	Panel C Overall survival
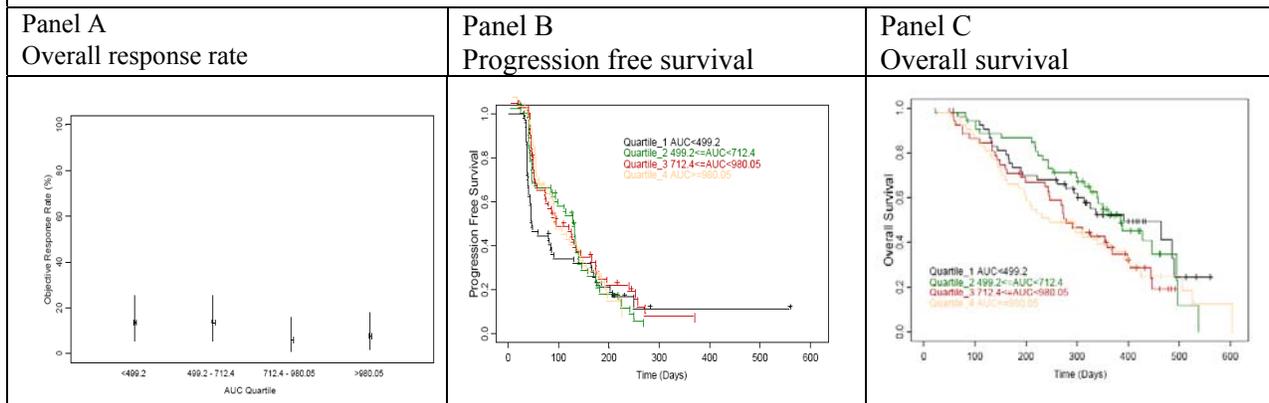
Source: figures 24, 26-27, page 65-68, pooled-pop-pkpd

AUC = μg*hr/L; AUC data was obtained after the first clinical dose of eribulin and the response was documented from the entire treatment period.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

There is a trend for an increased incidence of grade 3/4 neutropenia and grade 3/4 febrile neutropenia with increasing exposures in patients with locally advanced or metastatic breast cancer in study 211 following clinical doses of 1.4 mg/m^2 (**Figure 2**). Binary logistic regression models were used to explore the relationship between exposure and adverse events (AEs). Neutropenia and febrile neutropenia are the common treatment emergent AEs for eribulin. Data from 169 patients were used in the analysis. Patients with elevated levels of aspartate transaminase (AST) had higher sensitivity to experience neutropenia. At the same exposures, patients with elevated AST had higher incidence of grade 3/4 neutropenia (**Figure 3**).

Figure 2. The probability of patients with Grade 3/4 neutropenia (left panel) and Grade 3/4 febrile neutropenia (right panel) in study 211 following clinical doses of 1.4 mg/m^2.
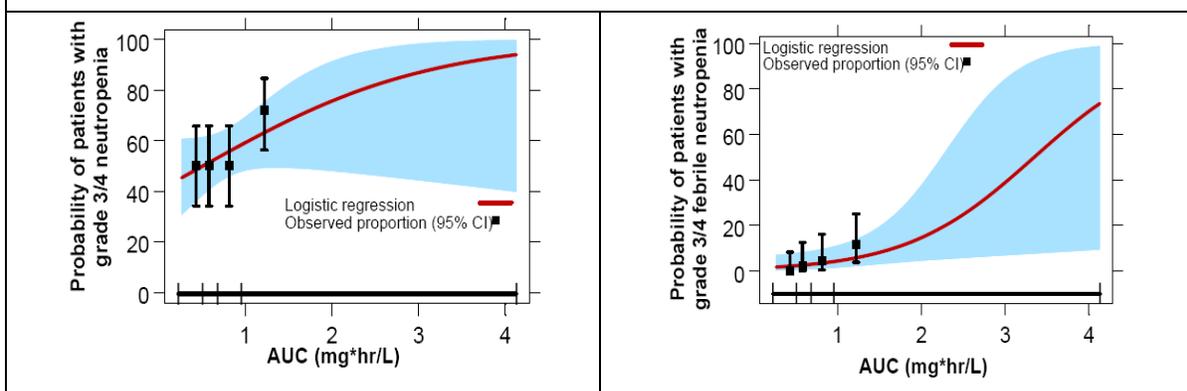
Source: figure 2, PM Review. AUC data was obtained after the first clinical dose of eribulin and the AEs were documented during the entire treatment period. Solid black symbols represent the observed proportion of patients experiencing adverse events in each AUC quartile. The vertical black bars represent the 95% CI. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% CI of the prediction. The exposure range in each AUC quartile is denoted by the horizontal black line.

Figure 3. The proportion of patients with grade 3/4 neutropenia vs. AUC for different levels of AST.
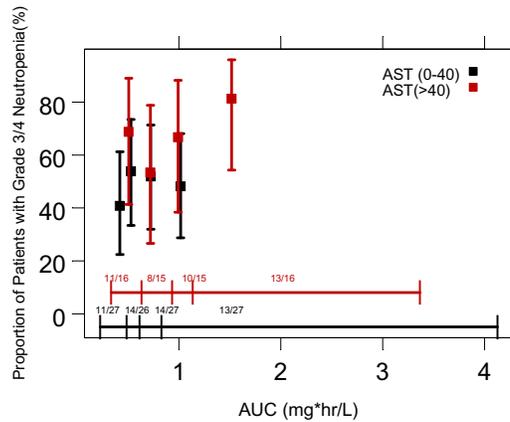
Source: figure 12, PM Review; AUC data was obtained after the first clinical dose of eribulin and the AEs were documented during the entire treatment period. Symbols represent the observed percentage of patients experiencing adverse events in each AUC quartile. The vertical black bars represent the 95% CI. The exposure range in each AUC quartile is denoted by the horizontal line.

The Pharmacometrics PK/AE analysis indicates that there is an increased incidence of grade 4 neutropenia with increasing exposures (**Figure 4**, left panel). No effect of AUC on the probability of patients with grade 2/3/4 neuropathy was observed (p=0.82) (**Figure 4**, right panel). See the Pharmacometrics Review for additional details.

Figure 4. The probability of patients with Grade 4 neutropenia (left panel) and Grade 2/3/4 neuropathy (right panel) vs. AUC of eribulin.
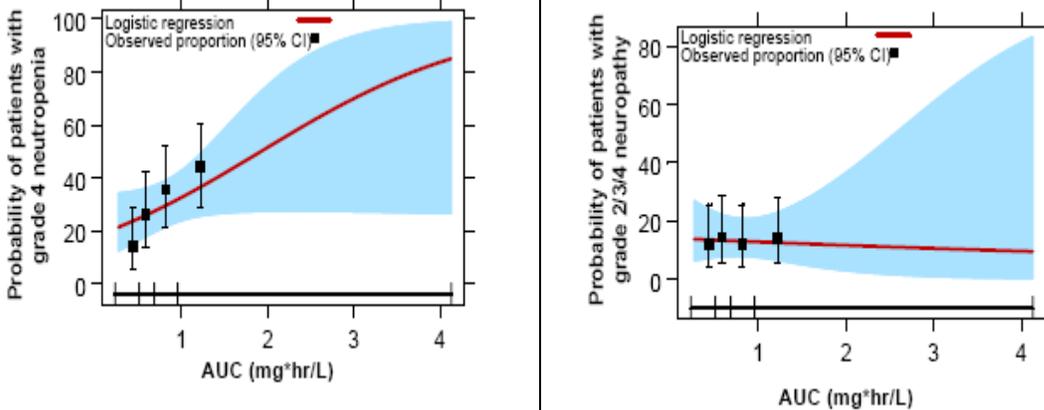
Source: figure 11, PM Review. AUC data was obtained after the first clinical dose of eribulin and the AEs were documented during the entire treatment period. Solid black symbols represent the observed percentage of patients experiencing adverse events in each AUC quartile. The black bars represent the 95% CI. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% CI. The exposure range in each AUC quartile is denoted by the horizontal black line.

2.2.4.3 Is the proposed dose adjustment for patients with adverse events appropriate?

Based on the analysis of E-R relationship conducted using data from study 211, a 50% dose reduction from 1.4 mg/m^2 to 0.7 mg/m^2 will not result in a significant reduction in grade 3/4 neutropenia. The applicant proposed to reduce the dose from 1.4 mg/m^2 to 1.1 mg/m^2 if patients experience grade 3 or 4 neutropenia (see **Table 9**). Further dose reduction to 0.7 mg/m^2 is proposed if grade 3 or 4 neutropenia re-occurs. The logistic regression model shows that decreasing the dose from 1.4 mg/m^2 to 1.1 mg/m^2 reduces the probability of grade 3/4 neutropenia from 55% to 52%. A dose reduction to 0.7 mg/m^2 further reduces the probability of grade 3/4 neutropenia to 48% (see **Table 10**). However, this analysis is limited by the data from a single phase 2 trial because PK samples were not collected in the registration trial (study 305).

In study 305, eribulin related grade 3 neutropenia and grade 4 neutropenia occurred in 21% and 24% of the patients, respectively. In the eribulin arm, 23% of the patients experienced dose delays or dose reductions or discontinued treatment due to neutropenia. Eighteen percent (18%) of the patients received G-CSF in the eribulin arm. As the E-R analysis shows that dose reduction alone will not reduce the risk of neutropenia significantly, it is likely that dose reduction together with dose delays and G-CSF administration will clinically manage neutropenia.

According to Dr. Donoghue (Clinical Reviewer), neutropenia was managed reasonably well in the registration trial.

2.2.4.4 Does this drug prolong the QT or QTc interval?

Dedicated QT Trial: An uncontrolled, open-label, multi-center, single arm dedicated clinical trial was conducted to determine the effects of eribulin mesylate on cardiac repolarization in 26 patients with solid tumors (E7389-E044-110). Eribulin 1.4 mg/m^2 was administered as an IV bolus given over 2-5 minutes on the morning of Days 1 and 8 of a 21-day cycle. On Days 1 and 8 of cycle 1, repeat continuous ECG digital Holter recordings and triplicate 12-lead ECGs were obtained and blood samples were collected pre-infusion and post-infusion at the following specific time-points that coincided with the ECG time points: 15 min, 30 min, 1, 1.5, 2, 3, 4, 5, 6 and 10, 24 and 48 hours after eribulin administration. The applicant stated that the sample size for the trial was primarily based on feasibility considerations; however, it was estimated that a sample size of 22 patients would ensure an 80% power when mean QTcF change from baseline was 10 ms, with a standard deviation of 18 milliseconds (msec).

A delayed prolongation in QTc interval was observed upon administration of 1.4 mg/m^2 of eribulin on Days 1 and 8 of a 21 day cycle in this trial (**Figure 5**). The maximum mean QTcF change from baseline (95% upper CI) was 11.3 (18.2) ms on day 8 (See the QT-IRT review for more details). The QTc prolongation is not concentration-dependent as there appeared to be no increase in QTcF with increasing drug concentrations (**Figure 6**).

The applicant is encouraged to explore the mechanism of the delayed effect on the QTc interval, and conduct a nonclinical biodistribution study to detect a delay in distribution of eribulin to the myocardium.

Figure 5. Scatter plot of QTcF change from baseline (ΔQTcF) vs. eribulin concentration on day 1 (left panel) and day 8 (right panel) of the dosing cycle.
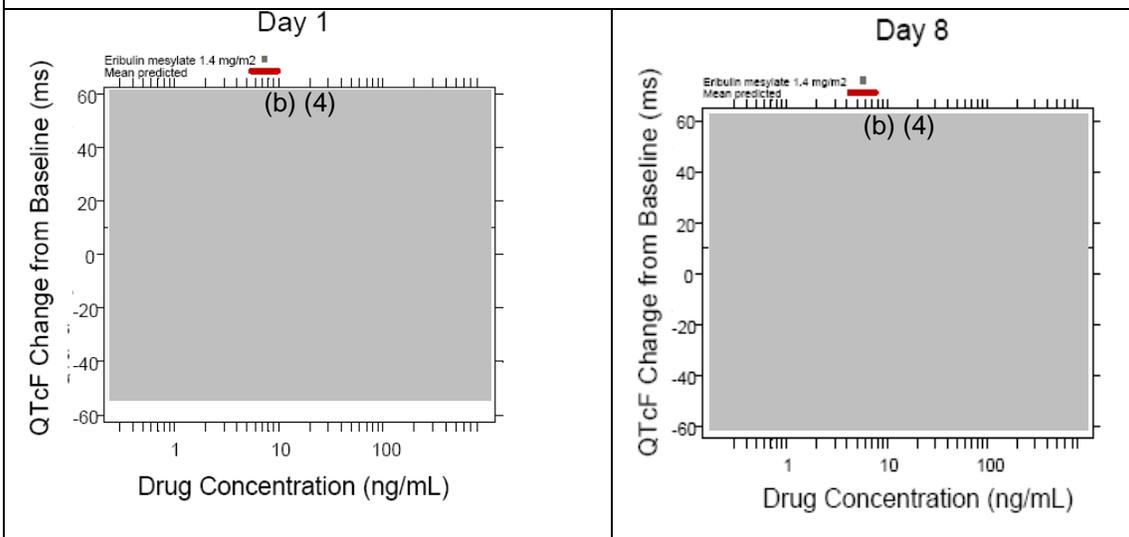
Source: figure 3, PM Review. Solid red line represents the mean predicted ΔQTcF. Black line represents a ΔQTcF of 10 ms.

Figure 6. Mean and one-side 95% CI of QTcF change from baseline vs. time profile per protocol population
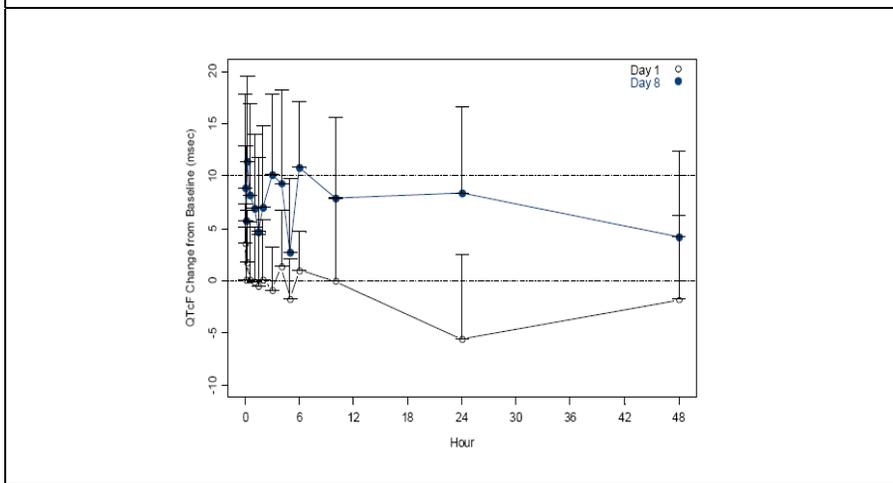
Source: figure 1, page 83 , E7389-E044-110 study report

ECG Evaluations in Clinical Trials: ECG evaluations were included as a safety variable for patients enrolled into nine clinical trials in addition to the dedicated QT trial (**Table 3**). ECG evaluations were conducted in study 103, 108 and 109, but the evaluations were categorized as normal, abnormal not clinically significant, abnormal clinically significant and not applicable.

Table 3. Summary of the ECG evaluations collected in the clinical pharmacology and clinical trials

Study Number	Day of Evaluation	ECG Evaluation[1]
101	baseline to trial termination	ΔQTcF -3.8 (14.8) msec
102	baseline to trial termination	ΔQTcF 8.2 (36.3) msec
105	Cycle 1, Day 9 Dose of 0.7 mg/m^2	CTCAE[2] Grade 2 QT prolongation n = 1 (QTc > 0.47 – 0.50 sec or ≥ 0.06 sec above baseline)
201	baseline to trial termination	ΔQTcF 5.4 (16.8) msec
211	baseline to trial termination	ΔQTcF 4.2 (22.1) msec
305	baseline to trial termination	ΔQTcF 2.2 (23.0) msec

[1] mean (SD)
[2] Common Toxicity Criteria for Adverse Events version 3.0

QT Evaluations in Nonclinical Studies: Three non-clinical studies suggest that eribulin has no potential for QTc prolongation at clinically relevant concentrations. The preclinical concentrations examined exceed the human plasma concentrations reported at the proposed dose by 5- to 136-fold.

An *in vitro* study examined the effects of eribulin on hERG tail current recorded from human embryonic kidney 293 (HEK293) cells stably transfected with hERG cDNA (Study No. SPH03-001) and demonstrated that treatment with 30 μM (22 μg/mL) eribulin produced no inhibition of hERG tail current.

An *in vitro* study examined the effects of perfusion of eribulin mesylate at concentrations of 1, 10 and 30 μM on intracellularly recorded action potential parameters in the isolated dog Purkinje fiber preparations and demonstrated no effect of eribulin on the evoked action potentials (Study No. SPP03-002).

A preclinical *in vivo* study demonstrated that beagle dogs did not experience ECG abnormalities after the administration of a 1-hour continuous infusion once a day on Days 1, 8 and 15 (Q7D×3) at doses of 0, 0.0045, 0.015 or 0.045 mg/kg (0, 0.09, 0.30 or 0.90 mg/m^2), followed by a 14-day recovery period, as part of a chronic intravenous toxicity study (Study No. 6288). Intravenous infusions of 0.01 mg/kg had no significant effect on the cardiovascular system, but intravenous infusions of 0.04 mg/kg transiently decreased the systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and heart rate and increased the RR interval. No ECG change was observed after repeat dosing.

2.2.4.5 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?

Final Dose Selection: The dose selection of 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle, based on efficacy and safety during Phase 1 and 2 clinical trials appears acceptable. This dosing regimen demonstrated improved OS in the registration trial and the major (>50%) treatment emergent adverse events (TEAE), including asthenia and/or fatigue, neutropenia, peripheral neuropathy, and alopecia, were manageable. Conclusive E-R relationships for efficacy and safety could not be established due to trial design limitations - single arm clinical trial at a single dose level, in a supportive phase 2 clinical trial, in which sparse PK samples were collected after the

first clinical dose. No PK samples were collected in the registration trial.

Dose Selection Trials: The initial recommended phase 2 dose (R2PD) of 1.4 mg/m^2 every week (QW) on Days 1, 8, and 15 of a 28-day cycle was based on the maximum tolerated dose (MTD) identified in a single dose escalation clinical trial. The MTD was defined as 1.4 mg/m^2 administered as an intravenous bolus in study NCI-5730 and the dose-limiting toxicities (DLTs) were alkaline phosphatase elevation and febrile neutropenia.

Comparison of a 21-day and 28-day Cycle: Eribulin mesylate was initially administered at a dose of 1.4 mg/m^2 as an intravenous bolus on Days 1, 8, and 15 of a 28-day cycle to patients enrolled into a subsequent phase 2 clinical trial. Seventy-one percent (71%) of patients enrolled received eribulin administered as a 28-day schedule and 33% received eribulin administered as a 21-day schedule. Dose interruptions, delays, and omissions were needed for 63% of patients during cycle 1 and in 54% of patients during cycle 2. The major TEAE were neutropenia and fatigue for patients administered eribulin as a 28-day schedule and 21-day schedule. The dosing regimen was subsequently modified to a dose of 1.4 mg/m^2 as an intravenous bolus on days 1 and 8 of a 21-day cycle in study 105.

Confirming Final Dose Selection: This dosing regimen of 1.4 mg/m^2 as an intravenous bolus on Days 1 and 8 of a 21-day cycle was subsequently employed in study 211 and study 305 (**Table 4**).

Table 4. Summary of the confirmation of the final dose selection

| Study Number	Treatment	Population (n)	Effectiveness	Adverse Events
211	1.4 mg/m^2 as an i.v. bolus on Days 1 and 8 of a 21-day cycle dose intensity 0.86 mg/m^2/week	299	ORR, 9% (95% CI: 6.1, 13.4) Duration, 126 days (95% CI: 89, 177).	dose delays, 54% dose reduction, 26% asthenia/fatigue, 65% alopecia, 60% neutropenia, 60% (32%)[1] neuropathy 24% (6%)[2] febrile neutropenia, 6%
305	1.4 mg/m^2 as an i.v. bolus on Days 1 and 8 of a 21-day cycle dose intensity 0.85 mg/m^2/week	762	OS 399 vs. 324 days (95% CI: 360, 434) (95% CI: 282, 380) PFS 113 vs. 68 days (95% CI: 101, 118) (95% CI: 63, 103) RR 12% vs. 5% (95% CI: 9.4, 16) (95% CI: 2.3, 8.4)	dose delays, 49% dose reduction, 29% asthenia/fatigue, 54% neutropenia, 52% (24%)[1] alopecia, 44% neuropathy 35% (8%)[2] febrile neutropenia, 6%

[1] Grade 4
[2] Grade 3 and 4

No unresolved dosing and administration issues have been identified.

Also see <u>section 2.2.1</u>.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

The applicant stated the best model to describe the concentration vs. time profile for eribulin was a three compartment model with linear elimination.
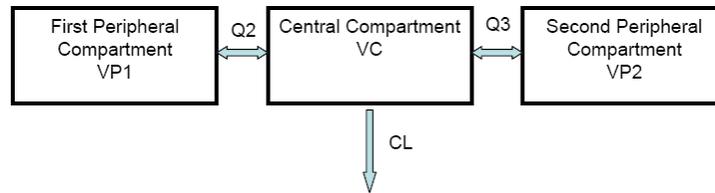
There are no major metabolites with clinically meaningful exposure for eribulin.

### 2.2.5.1 What are the single dose and multiple dose PK parameters?

The PK parameters of eribulin following administration of a single dose were characterized in seven clinical trials (**Table 5** and **Table 6**) and following administration of multiple doses in three clinical trials (**Figure 7** and **Table 6**).

Single Dose Pharmacokinetic Parameters:

Table 5. Summary of pharmacokinetic parameters after single dose administration							
Study	**N**	**Dose** (mg/m^2)	**C_{max}** (ng/ml)	**t ½** (hours)	**$AUC_{(0-\infty)}$** (ng*h/mL)	**CL** $(L/h/m^2)$	**V_{ss}** (L/m^2)
102 One hour intravenous infusion	1	0.25	44	35.2	138	1.60	53.3
	4	0.50	63 (29)	34.4 (20)	210 (26)	2.22 (26)	67.6 (37)
	3	1.0	127 (31)	45.9 (48)	486 (68)	2.42 (57)	86.7 (13)
	7	2.0	369 (10)	48.8 (45)	1842 (46)	1.16 (47)	47.8 (21)
	3	2.8	340 (39)	42.3 (16)	1412 (44)	2.12 (59)	87.4 (56)
	3	4.0	528 (34)	66.0 (33)	2334 (27)	1.70 (44)	114.2 (14)
103 Intravenous bolus	6	2mg	444 (36)	45.6 (17)	681 (68)	1.82 (40)	68.6 (20)
108 Intravenous bolus	6	1.4	186 (26)	36.1 (24)	600 (23)	2.33 (31)	84.6 (42)
109 Intravenous bolus	10	1.4	207 (36)	45.6 (30)	971 (54)	1.55 (51)	77 (43)
Source: table 6, page 23, summary-clin-pharm nd = not determined Mean (CV%)							

Multiple Dose Pharmacokinetic Parameters: The PK parameters of eribulin following administration of multiple doses were estimated following the collection of blood in three clinical trials (**Figure 7** and **Table 6**).

Figure 7. Mean eribulin plasma concentration-time profile following administration of 1.4 mg/m^2 on day 1 and day 8
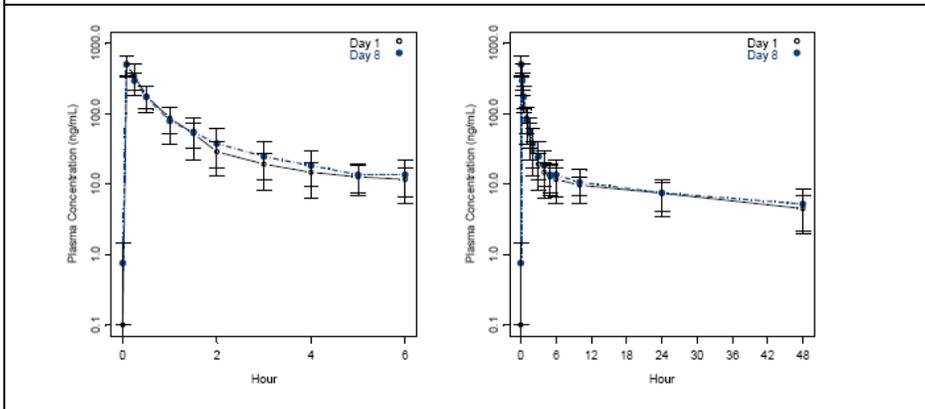
Source: figure 19, page 80, summary-clin-pharm

The PK parameters were calculated by non-compartmental analysis on day 15 of the first cycle for study 101 and on day 8 of the first cycle for study 105 and study 110. Study 110 is not listed in the table below, since only the C_{max} was recorded for each day. Only the PK parameter estimates from the PK samples collected during study 105 are relevant, since eribulin was administered at the proposed clinical dose and schedule.

Table 6. Summary of clinical pharmacology clinical trials after multiple dose administration

			Day 1				Day 8 (study 105) or 15 (study 101)			
Study	**N**	**Dose (mg/m^2)**	**Cmax (ng/ml)**	**t ½ (hours)**	**AUC(0-∞) (ng h/mL)**	**CL (L/h/m^2)**	**Cmax (ng/ml)**	**t ½ (hours)**	**AUC(0-∞) (ng h/mL)**	**CL (L/h/m^2)**
101	2	0.25	44 (nd)	32.1(nd)	173 (nd)	1.93 (nd)	106 (nd)	27.6 (nd)	228 (nd)	1.70 (nd)
	7	0.50	79 (41)	38.0 (72)	338 (71)	1.90 (60)	80 (59)	41.0 (35)	642 (130)	1.98 (77)
	4	0.70	117 (36)	35.8 (52)	512 (58)	1.51 (49)	112 (36)	27.4 (17)	526 (93)	1.89 (61)
	9	1.0	144 (30)	40.5(37)	653(57)	1.92 (70)	127 (22)	32.7 (40)	412 (42)	2.50 (44)
	9	1.4	233 (41)	37.2 (25)	856 (44)	1.73 (45)	247 (41)	35.6 (52)	913 (76)	1.88 (52)
105	3	0.7	289 (15)	36.4 (31)	299 (42)	2.31 (38)	313 (25)	37.8 (30)	336 (29)	1.97 (34)
	3	1.0	381 (14)	42.9 (25)	380 (17)	2.37 (17)	453 (20)	36.7 (12)	418 (18)	2.17 (19)
	6	**1.4**	**519 (21)**	**39.4 (21)**	**673 (17)**	**1.89 (18)**	**544 (10)**	**38.6 (14)**	**699 (18)**	**1.82 (18)**
	3	2.0	718 (15)	59.9 (22)	1370 (21)	1.32 (19)	nd	nd	nd	nd

Source: table 8, page 26, summary-clin-pharm

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable. All trials with eribulin were conducted in patients with solid tumors due to the highly toxic nature of the drug substance.

2.2.5.3 What are the characteristics of drug absorption?

Not applicable. The proposed dose of eribulin is 1.4 mg/m^2 administered as an intravenous bolus over 2 to 5 min weekly on Days 1 and 8 of a 21-day cycle.

2.2.5.4 What are the characteristics of drug distribution?

The PK of eribulin is characterized by a rapid distribution phase.

Protein Binding: The applicant conducted an *in vitro* plasma protein binding study using an equilibrium dialysis method (DSD-2001-38). Protein binding was calculated according to the following equation:

$$\text{\% protein binding} = 100 - [C_f / (C_p-C_f)(V/V_0) + C_f] *100$$

where C_f is the concentration in buffer post-dialysis; C_p is the concentration in the plasma post-dialysis; V_o is the volume of plasma pre-dialysis and V is the volume of plasma post-dialysis, respectively. The mean plasma protein binding of eribulin ranged from 49% to 65% between 100 ng/mL and 1000 ng/mL (**Table 7**).

Table 7. Protein binding of eribulin in human plasma following a two-hour dialysis

Conc. ng/mL	C_p	C_f	V	V_o	% Free	% bound	Mean ± SD
	53.17	18.55	1.000	1	34.88	65.12	65.07±3.79 [a,b]
	47.56	18.17	1.000	1	38.21	61.79	
100	49.88	17.90	0.920	1	37.82	62.18	
	52.49	18.02	0.970	1	35.01	64.99	
	56.54	16.25	1.000	1	28.75	71.25	
	238.64	158.32	0.940	1	67.71	32.29	48.92±13.24 [a,b]
	177.54	105.07	0.850	1	63.04	36.96	
500	219.95	94.58	1.020	1	42.51	57.49	
	212.13	89.52	0.970	1	42.95	57.05	
	228.54	90.59	1.020	1	39.16	60.84	
	429.66	184.05	0.910	1	45.16	54.84	50.03±6.90 [a]
	433.24	198.11	0.950	1	47.00	53.00	
1000	433.24	245.22	0.900	1	59.17	40.83	
	381.37	203.53	0.925	1	55.30	44.70	
	501.87	209.32	0.940	1	43.22	56.78	

Source: table 5, page 26, dsd-2001-38

Volume of Distribution: The mean volume of distribution at steady-state (V_{ss}) after intravenous administration of eribulin ranged from 43 L/m^2 to 114 L/m^2 across trials. This volume of distribution exceeds total body water and suggests that eribulin extensively distributes into tissues. See section 2.2.5.1.

P-Glycoprotein (Pgp): In vitro studies (CAIVT0105 and CAIVT0106) suggest that eribulin is a Pgp substrate and an inhibitor (DDD-2008-06). See section 2.4.2.4.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

An open-label, non-randomized, single center trial was conducted in six patients diagnosed with advanced solid tumors to determine the metabolism and elimination of radiolabeled eribulin (study no. E7389-E044-103). Following administration of a radiolabeled fixed dose of 2 mg of eribulin, the major route of excretion was fecal (82% of the dose). The mean total recovery of the radioactive dose in urine and feces was 90% (range 76% to 111%). Unchanged eribulin accounted for most of the total radioactivity (88%) excreted in the feces up to 72 h post dose. The mean cumulative dose recovery of the total radioactivity in the urine was 8.9% (range 5.4% to 16.4%). Eribulin represented most (~91%) of the total radioactivity excreted in the urine. Although it cannot be directly measured in patients, biliary excretion likely substantially contributes to eribulin clearance. Eribulin undergoes minimal hepatic metabolism and it is

excreted predominantly in the feces. A preclinical ADME study showed that 36% of the administered dose was recovered in bile at 72 hours following the administration of a radiolabeled dose to male rats (study no. CFG13996).

2.2.5.6 What are the characteristics of drug metabolism?

Table 8 lists the nonclinical studies conducted by the applicant that used human biomaterials.

Table 8. Summary of *in vitro* studies using human biomaterials for eribulin		
Study Number	**Study Objective**	**Study outcome**
CAIVT0102	To determine the antiproliferative effects of eribulin against paclitaxel resistant human cancer cells based on acquired mutations in β-tubulin	Cell growth
CAIVT0105	To determine whether eribulin is susceptible to drug resistance based on Pgp-mediated drug efflux	Substrate
CAIVT0106	To determine whether eribulin is susceptible to drug resistance based on Pgp-mediated drug efflux	Substrate
DDD-2005-46	To evaluate the potential induction of cytochrome P450 2C enzymes using human hepatocytes	Induction potential
DDD-2008-06	To determine if eribulin was an inhibitor of Pgp	Inhibition potential
DSD-2003-01	To evaluate and characterize human hepatic metabolism to eribulin *in vitro*	Metabolic profile
DSD-2004-03	To evaluate the potential induction of human CYPlA and CYP3A by eribulin	Induction potential
DSDM-2005-45	To evaluate CYP-associated drug-drug interactions by eribulin using primary human hepatocytes	DDI potential
SPH03-001	To determine the effects of eribulin on hERG tail current recorded from stably transfected HEK2923 cells	hERG tail current

CYP3A4 Mediated Drug Metabolism: The metabolic stability study of eribulin in human liver microsomes suggests negligible metabolism of eribulin (DSD-2003-01). Eribulin 1 μM and 5 μM (2 μg/mL) were metabolized by only 15% in 30 min in pooled liver microsomes. Recombinant CYP3A4 metabolized 1 μM and 5 μM eribulin in 30 minutes by ~40% and 20%, respectively. CYP3A4-specific inhibitors reduced the metabolism of eribulin by recombinant CYP3A4 supporting the potential of CYP3A4 to metabolize eribulin. The main metabolites that were identified were isomeric monohydroxylates. No metabolism of eribulin was detected after incubated with subcellular fractions of human liver or cDNA expressed recombinant enzymes indicating eribulin is not likely metabolized by other phase I or phase II metabolic enzymes. These data indicate that the limited metabolism that eribulin undergoes appears to be mediated by CYP3A4.

In vivo Drug Metabolism: The data from the mass balance trial demonstrated that there were low levels of circulating metabolites following the intravenous administration of eribulin. Eribulin accounted for near 100% of the radiolabeled concentrations in the plasma. About 90% of unchanged eribulin is excreted into the feces and urine. These data indicate that eribulin undergoes very limited metabolism in humans.

A drug-drug interaction trial with the strong CYP3A4 inhibitor, ketoconazole demonstrated that the AUC was similar with and without the coadministration of the inhibitor (study 109). The applicant also demonstrated in the population PK analysis that the coadministration of CYP3A4 inducers and inhibitors would not be expected to affect eribulin exposure. See section 2.4.2.2.

2.2.5.7 What are the characteristics of drug excretion?

The data from the mass balance trial indicates that eribulin undergoes negligible metabolism. Plasma eribulin concentrations accounted for nearly 100% of the radioactive concentrations in the plasma and ~90% of the dose is excreted unchanged in the urine and feces. Approximately 82% of the radioactive dose was excreted in the feces, of which 88% represented unchanged parent drug.

Three dose-escalation trials showed minimal renal elimination of eribulin, with < 9% of the dose recovered in urine. The data from the mass balance trial confirmed that renal elimination of eribulin is a minor route for eribulin excretion. The mean cumulative dose recovery of total radioactivity in the urine was 8.9%, of which 91% represented unchanged parent drug.

Eribulin demonstrates low plasma clearance after intravenous administration, with the mean clearance ranging from 1.0 L/h/m^2 to 2.4 L/h/m^2 across trials. Renal clearance (0.14 L/h/m^2) represented a minor component (<10%) of total clearance of eribulin (1.8 L/h/m^2) in the mass balance trial.

Mild and moderate hepatic impairment increased the exposure to eribulin as demonstrated in the dedicated hepatic impairment trial. The population PK analysis shows that eribulin clearance is affected by serum albumin, alkaline phosphatsase and bilirubin levels.

The mean terminal half-life of eribulin was reported by the applicant as approximately 40 hours. Our analysis indicates the mean geometric elimination half-life was 37, 43 and 42 hours in study 101, study 102 and study 105, respectively, with an overall geometric mean half-life of 40 hours.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

The AUC$_{0-inf}$ of eribulin was dose-related over the dose range studied (0.25 mg/m^2 to 4.0 mg/m^2) (**Figure 8**). This analysis was not conducted for C$_{max}$, since only one of the 3 dose escalation trials used a bolus administration. Our analysis confirms that the AUC is dose linear following the administration of an intravenous infusion in study 101 and 102 and following the administration of an intravenous bolus in study 105.

Figure 8. Effect of dose on AUC pooled across dose-rising trials 101, 102 and 105 (panel left) and for study 105 (panel right).
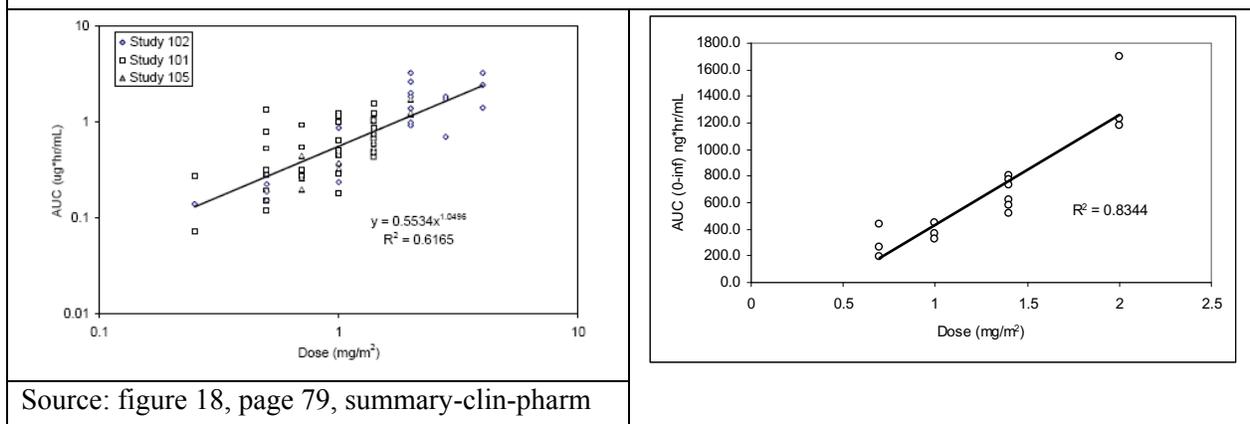
Source: figure 18, page 79, summary-clin-pharm

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Accumulation: The AUC was similar on days 1 and 8 or 15 in these clinical trials (see **Table 6**). Given the mean $t_{1/2}$ of eribulin is 40 hours and the weekly dosing interval, no considerable accumulation is expected. See Section 2.2.5.1.

Time Independence: Individual patient PK parameters after multiple dosing, on the second or third weekly dose of the first cycle, were comparable to PK after a single dose, indicating no time-dependent changes in the PK of eribulin (see **Table 6**). See Section 2.2.5.1.

2.2.5.10 What are the inter- and intra-subject variability of PK parameters in healthy volunteers and patients, and what are the major causes of variability?

Eribulin was not administered to healthy volunteers; no PK samples are, therefore, available.

The interindividual variability in the clearance of eribulin was 54%. The variability was reduced to 46% when weight and albumin, alkaline phosphatase and bilirubin levels were added as covariates. The interoccasion variance was reduced from 15% to 14%. The remaining unexplained variability in the PK model is still high, suggesting the model should only be used for supportive evaluation for dose adjustments rather than as a primary tool to guide dose adjustments.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The influence of age, gender, race, weight, renal impairment, hepatic impairment, and concomitant medications on the systemic clearance of eribulin was evaluated as part of the applicant's population PK analysis. The applicant stated that eribulin clearance was found to be affected by weight and albumin, alkaline phosphatase and bilirubin levels.

Genetic Polymorphisms: Genotype for *CYP3A* was determined in 30 Whites enrolled in three

clinical trials. Most patients in these clinical trials were *CYP3A4* extensive metabolizers and *CYP3A5* non-expressers. The limited sequence variability prohibited the exploration of a relationship between genotype and eribulin clearance. In addition, it is not understood why the applicant identified the *CYP3A* genotype in these trials, since eribulin undergoes negligible metabolism. See the genomics review for additional information.

Organ Dysfunction: A dedicated hepatic impairment trial was conducted in patients with mild or moderate hepatic impairment as compared to patients with normal hepatic function. A dose reduction to an initial dose of 0.7 mg/m^2 administered as intravenous bolus is proposed for patients with moderate hepatic impairment. Our analysis indicates that a reduction to an initial dose of 1.1 mg/m^2 should also be recommended for patients with mild hepatic impairment (see **Table 12** and **Figure 15**). The clinical trial did not enroll patients with severe hepatic impairment and the applicant ████████████ (b) (4) ████████████

A dedicated renal impairment trial was not conducted, but in our Pharmacometrics population PK analysis, a slight trend was observed between creatinine clearance (CL$_{CR}$) and clearance (CL) for patients with mild and moderate renal impairment (see **Figure 13**). Our non-compartmental analysis shows that the geometric mean dose-normalized exposure increased approximately by 2-fold in patients with moderate renal impairment. Therefore, we recommend a lower starting dose of at least 1.1 mg/m^2 in patients with moderate renal impairment (see **Figure 14**). We recommend a PK trial in patients with severe renal impairment to ████ (b) (4) ████████

Intrinsic Factors on Safety Profile: Age, gender and race were not predictive of the probability of experiencing neuropathy or neutropenia. A relationship was identified between neutropenia and exposure in four clinical trials. The probability of grade 4 neutropenia also appears to increase with increasing AST levels at similar exposures. The applicant stated that the probability of a patient experiencing Grade 3 neuropathy appeared to be cumulative with the probability being low in the first cycle of treatment regardless of the AUC of eribulin and slowly increased with increasing treatment cycles at higher exposures. See section 2.2.4.1 and 2.2.4.2.

Our Pharmacometrics analysis identified a trend for increased incidence of grade 3-4 neutropenia and grade 3-4 febrile neutropenia with increasing exposure. This analysis also demonstrated no evidence of an increase probability of grade 2-4 neuropathy with increasing exposure in the same data set. The data is, however, limited by the patients enrolled into a single phase 2 trial and who provided sparse blood samples for PK analysis after a single clinical dose.

2.3.2 **Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

Hepatic Impairment: The applicant proposed a lower starting dose for patients with moderate hepatic impairment. A 50% dose reduction to an initial dose of 0.7 mg/m^2 administered as intravenous bolus is recommended for patients with moderate hepatic impairment based on 2.3-fold increase in geometric mean dose-normalized exposure as compared to patients with normal hepatic function. We recommend an initial dose of 1.1 mg/m^2 for patients with mild hepatic impairment based on a 1.7-fold increase in geometric mean dose-normalized exposure as

compared to patients with normal hepatic function.

Renal Impairment: We recommend a dose reduction to an initial dose of 1.1 mg/m^2 for patients with moderate renal impairment. Our Pharmacometrics population PK analysis indicates a slight trend between creatinine clearance (CL$_{CR}$) and eribulin clearance (CL) for patients with moderate renal impairment. The median CL for subjects with moderate renal impairment was lower (1.6 L/hr) compared to normal subjects (3.3 L/hr). Data from 269 patients were used in the analysis. Thus, a 2-fold increase in the geometric mean dose-normalized AUC is observed for subjects with moderate renal impairment in a subset of patients in which dense PK samples were collected (n=77). We recommend a clinical trial to assess the effect of severe renal impairment on the PK of eribulin.

Toxicity: The dose recommendations proposed by the applicant for grade 3 or 4 hematological or non-hematological toxicity are listed in **Table 9**. Based on E-R relationship explored using data from study 211, a dose reduction from 1.4 mg/m^2 to 0.7 mg/m^2 will not result in considerable reduction in grade 3/4 neutropenia. The applicant proposed to reduce the dose from 1.4 mg/m^2 to 1.1 mg/m^2 if patients experience grade 3 or 4 neutropenia. Further dose reduction to 0.7 mg/m^2 is proposed if grade 3 or 4 neutropenia re-occurs (**Table 9**). The logistic regression model shows that decreasing the dose from 1.4 mg/m^2 to 1.1 mg/m^2 reduces the probability of patients experiencing grade 3/4 neutropenia from 55% to 52%. A dose reduction of 50% to 0.7 mg/m^2 reduces the probability of grade 3/4 neutropenia to 48%. Since the dose reduction from 1.4 mg/m^2 to 0.7 mg/m^2 only decreases the risk of grade 3/4 neutropenia by less than 8%, dose reduction alone is not sufficient for clinical management of neutropenia (**Table 10**). This analysis is limited to data from a single phase 2 trial in which sparse PK samples were collected in 211 patients and PK samples were not collected in the pivotal trial (study 305).

In study 305, eribulin related grade 3 neutropenia and grade 4 neutropenia occurred in 21% and 24% of the patients, respectively. In the eribulin arm, 23% of the patients had dose delays, dose reductions or discontinued treatment due to neutropenia. Eighteen percent (18%) of the patients received G-CSF in the eribulin arm. As the E-R analysis shows that dose reduction alone will not reduce the risk of neutropenia considerably, it is likely that dose reduction together with dose delays and G-CSF administration might be needed as part of the clinical management for this adverse event.

According to Dr. Donoghue (Clinical Reviewer), neutropenia was managed reasonably well in the pivotal trial.

Table 9.			(b) (4)		
		(b) (4)			(b) (4)
ANC <500 cells/mm³ lasting >7 days					
ANC <1,000 cells/mm³ complicated by fever or infection					1.1 mg/m²
Platelets <25,000/mm³					
Platelets <50,000/mm³ requiring transfusion					
Nonhematologic:					
Any Grade 3 or 4	(b) (4)			(b) (4)	1.1 mg/m²
	(b) (4)				0.7 mg/m²

Abbreviation: ANC, absolute neutrophil count.

[a] Toxicities graded in accordance with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Reactions (CTCAE).

Table 10. Reviewer's logistic regression results for dose reduction

Dose (mg/m²)	Median AUC (mg*hr/L)	Probability of patients with Grade 3/4 Neutropenia (%)	Probability of patients with Grade 3/4 Febrile Neutropenia (%)	Probability of patients with Grade 4 Neutropenia (%)
1.4	0.786	55.2	3.39	29.1
1.1	0.618	52	2.74	26.4
0.7	0.393	47.7	2.06	23.1

2.3.2.1 Pediatric patients

Safety and effectiveness have not been established in pediatric patients. The applicant requests a pediatric waiver. The justification provided included disease-specific indication for the treatment of a condition in adults. The **P**ediatric **R**eview **C**ommittee (PeRC) granted the waiver on May 5, 2010.

2.3.2.2 Elderly

The population PK analysis showed that eribulin disposition in the elderly (>65 year of age) does not differ from younger patients (**Figure 9**). The median clearance in the patients < 65 years of age is 2.86 L/h compared to 2.82 L/h in patients greater than or equal to 65 years.

Figure 9. Effect of age on clearance

Source: figure 14, page 47, pooled-pop-pkpd
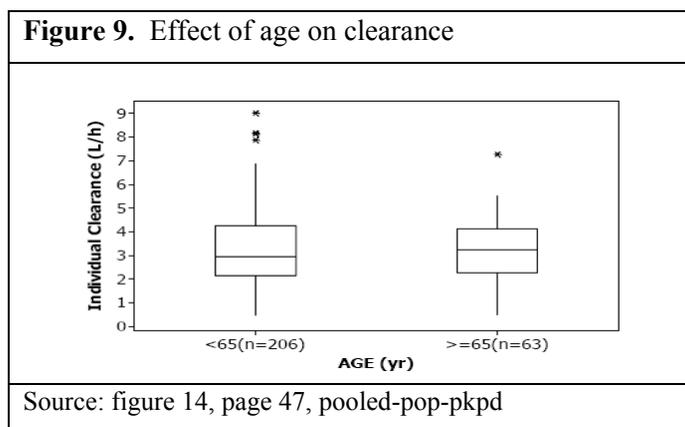
2.3.2.3 Gender

The population PK analysis showed gender did not influence the clearance of eribulin (**Figure 10**). The median clearance was 3.07 L/h in men and 2.80 L/h in women (P=0.10)

Figure 10. Effect of gender on clearance

Source: figure 13, page 47, pooled-pop-pkpd
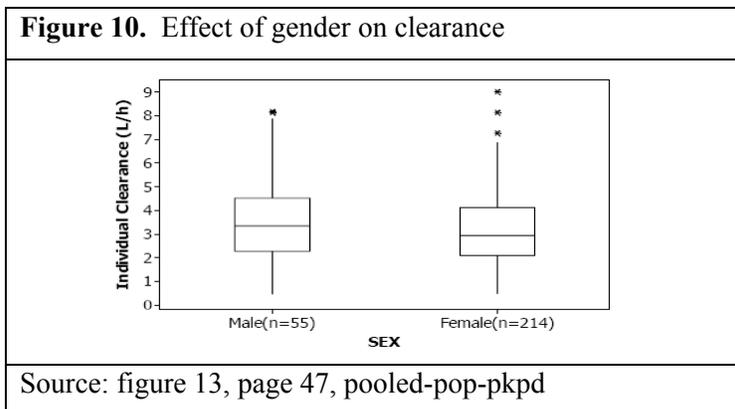
2.3.2.4 Race

The population PK analysis showed that race does not influence the clearance of eribulin (P=0.51). The race was not recorded or missing for 41 patients (**Table 11. Figure 11**).

Table 11. Median clearance of eribulin by race/ethnicity

Race	White	Black	Asian	Japanese	Hispanic	Other
Cl (L/h)	2.91	2.20	2.22	3.20	2.69	2.82

Figure 11. Effect of race/ethnicity on clearance

Source: figure 11, page 47, pooled-pop-pkpd
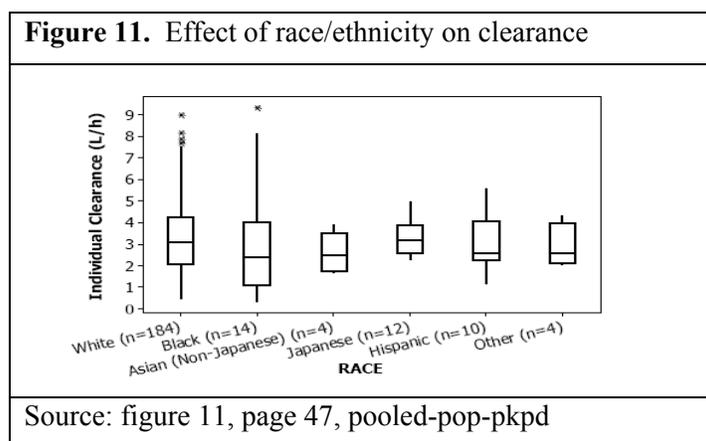
2.3.2.5 Body Size

Eribulin was administered using a dose corrected for body surface area. The applicant stated that clearance was found to increase with increasing weight accounted by an allometric relationship (**Figure 12**). This is supportive of dose individualizations using body surface area, since allometry and body surface area are similar metrics for body size. The applicant stated that there is a strong visual trend for increasing weight and increasing central volume of distribution.

Figure 12. Effect of weight on clearance (left panel) and central volume of distribution (right panel)
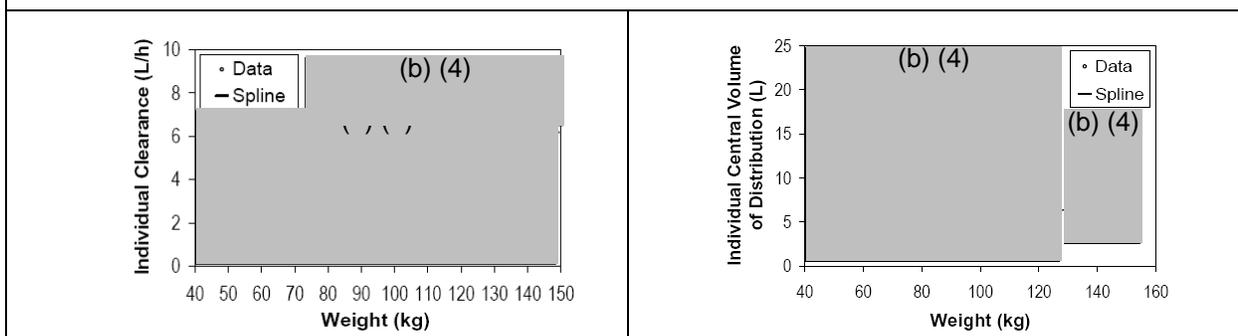
Source: figure 4, page 43, pooled-pop-pkpd and figure 16, page 49, pooled-pop-pkpd

2.3.2.6 Renal Impairment

The applicant concluded from their population PK analysis that renal function does not influence eribulin clearance. Our Pharmacometrics analysis indicates that a slight trend is observed between inter-individual variability on clearance and creatinine clearance (CL_{CR}) for patients with mild and moderate renal impairment (**Figure 13**). **Figure 13** shows that the median eribulin CL for subjects with moderate renal impairment was lower (1.6 L/hr) compared to normal subjects (3.3 L/hr). Thus, a 2-fold increase in median dose-normalized AUC is observed for subjects with moderate renal impairment. This implies that a larger effect is likely to exist for patients with severe renal impairment and thus needs to be further explored by the applicant.

Figure 13. Inter-individual variability on eribulin clearance (left panel) and eribulin clearance vs. creatinine clearance (right panel)
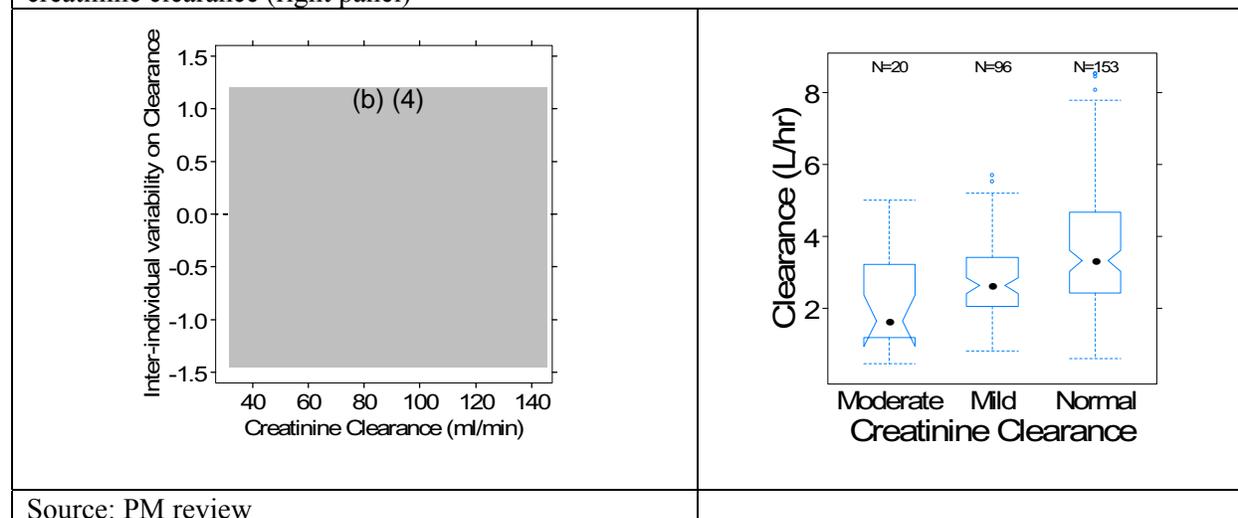
Source: PM review

We compared the geometric mean dose-normalized AUC for patients with normal renal function (n=44) and mild (n=27) and moderate (n=6) renal impairment enrolled into one of the six clinical pharmacology trials with dense PK sampling. These 77 patients are a subset of the population included in the applicant's and our Pharmacometrics population PK analysis. Our analysis demonstrated that the mean dose-normalized AUC increased 2-fold in patients with moderate impairment (**Figure 14**). In a clinical trial of 15 patients with renal dysfunction and advanced

urothelial cancer, a trend towards increasing AUC and decreasing clearance with worsening renal function was found (Synold TW, et al. Am Soc Clin Oncol 2010; abstract #2527). We recommend a lower starting dose of 1.1 mg/m^2 for patients with moderate renal impairment and that the applicant conduct a clinical trial to assess the effect of severe renal impairment on the PK of eribulin. We recommend a lower starting dose of at least 1.1 mg/m^2 for patients with severe renal impairment and the patients should be closely monitored.

Figure 14. Effect of renal impairment on the systemic exposure of all patients with dense PK sampling enrolled into a clinical pharmacology trial.

The black line represents the geometric mean systemic exposure for patients with normal renal function.
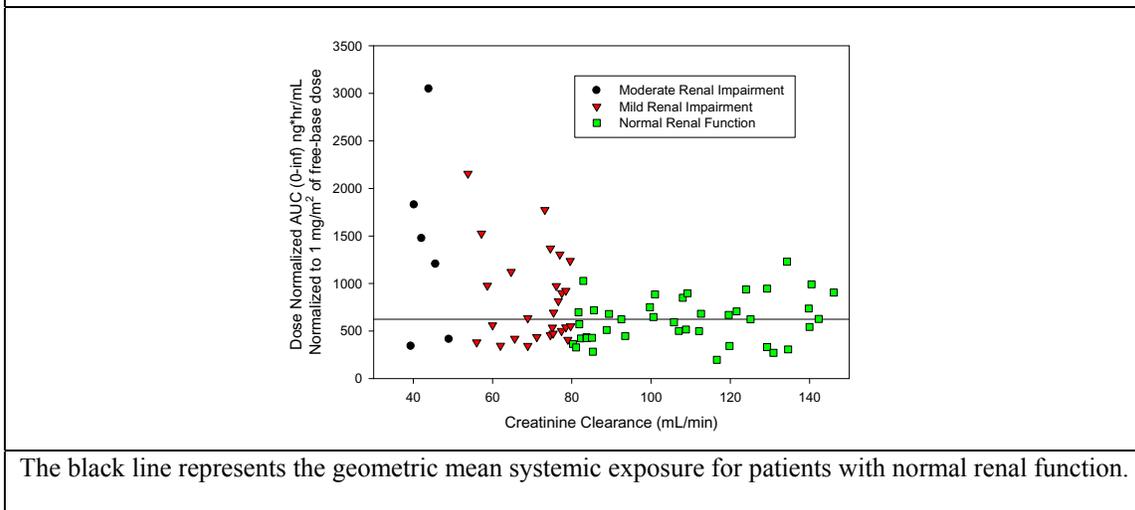
2.3.2.7 Hepatic Impairment

A dedicated hepatic impairment trial was conducted by the applicant in patients with mild and moderate hepatic impairment as compared to patients with normal hepatic function. Patients were assigned to one of three groups: normal hepatic function, mild hepatic impairment (Child-Pugh A) and moderate hepatic impairment (Child-Pugh B). Treatment with eribulin was given on Day 1 and the blood samples for PK assessment were collected before and after drug administration at specified time points. Patients with normal hepatic function received a dose level of 1.4 mg/m^2; patients with mild hepatic impairment received a dose level of 1.1 mg/m^2 and patients with moderate hepatic impairment received a dose level of 0.7 mg/m^2.

Hepatic impairment decreased clearance, prolonged the elimination half-life, and increased both AUC and Cmax of eribulin (**Table 12**). The applicant proposes a reduction to an initial starting dose of 0.7 mg/m^2 for patients with moderate hepatic impairment and we agree with this dose reduction. The geometric mean dose normalized AUC increased 1.7-fold in patients with mild hepatic impairment (**Figure 15**) and the probability of grade 4 neutropenia increases with increasing AST despite similar exposure. Based on these data, we recommend a reduction to an initial starting dose of 1.1 mg/m^2 for patients with mild hepatic impairment. Eribulin was not studied in patients with severe hepatic impairment; therefore, we agree with the applicant's proposed (b) (4) .

Table 12. Relative systemic exposure following the single administration of eribulin to patients with mild or moderate hepatic impairment as compared to normal hepatic function

Parameter	Geometric Least Square Means Impaired	Normal	Comparison	Ratio[a]	90% Confidence Interval
AUC(0-∞): ng·hr/mL/mg	390	223	Child-Pugh A: Impaired vs. Normal	1.75	(1.15 – 2.66)
	554		Child-Pugh B: Impaired vs. Normal	2.48	(1.57 – 3.92)
AUC(0-t): ng·hr/mL/mg	361	213	Child-Pugh A: Impaired vs. Normal	1.70	(1.15 – 2.51)
	453		Child-Pugh B: Impaired vs. Normal	2.13	(1.39 – 3.26)
Cmax: mg/mL/mg	80.2	69.9	Child-Pugh A: Impaired vs. Normal	1.15	(0.81 – 1.63)
	90.5		Child-Pugh B: Impaired vs. Normal	1.29	(0.89 – 1.89)

a: Ratio of treatment means was Impaired:Normal
Data were normalized to a dose of 1 mg

Source: table 2S, page 5, E7389-E044-108 clinical study report

Figure 15. Eribulin clearance (panel left) and dose-normalized AUC (panel right) stratified by hepatic function.

The lines indicate the geometric mean values.
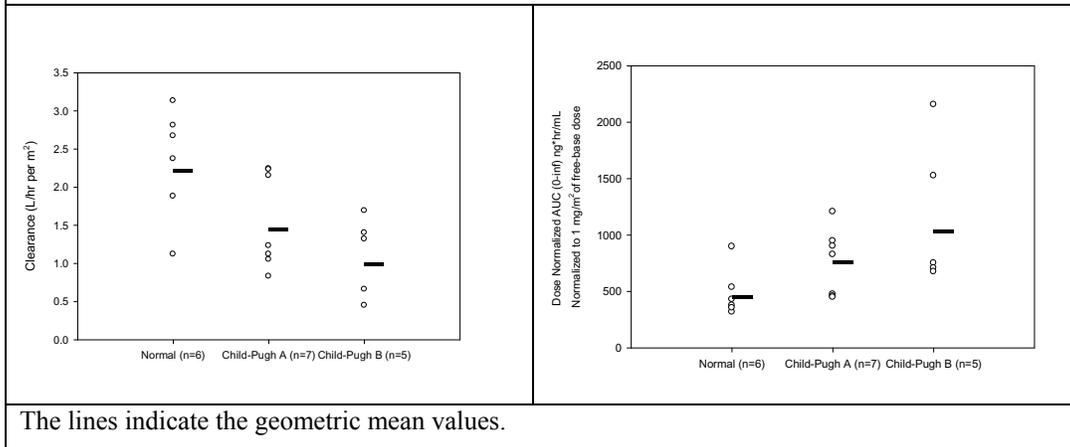
The population PK analysis indicated that weight and serum albumin, bilirubin and alkaline phosphatase levels influenced the clearance of eribulin and support the association found in the dedicated hepatic impairment trial (**Figure 16**).

Figure 16. Effect of serum albumin (left panel), bilirubin (middle panel) and alkaline phosphatase (right panel) on the clearance of eribulin
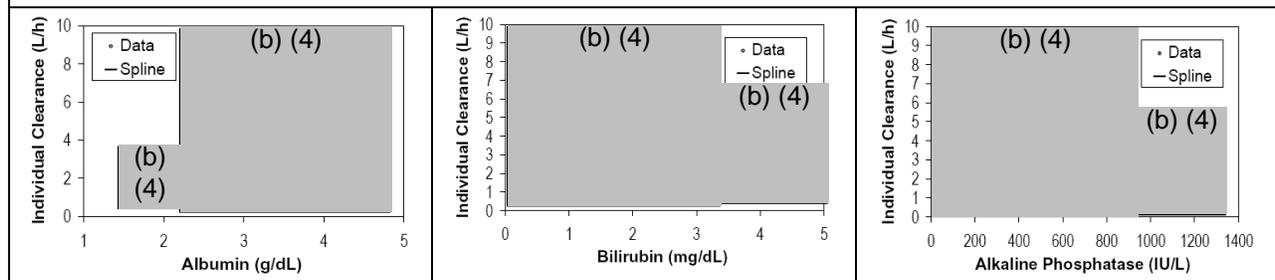
Source: figures 6–8, page 44-45, pooled-pop-pkpd

The applicant stated that cloud plots of grade of neutropenia, AUC and liver enzymes (ALT, AST and bilirubin) showed a somewhat tendency for higher numbers of grade 4 neutropenia for patients with elevated liver enzymes as compared to patients whose enzymes were within the normal range. In this analysis, the best predictor for neutropenia was AUC, with AST as a power function. See section 2.2.2.4.

2.3.2.8 What pregnancy and lactation use information is there in the application?

There are no adequate and well-controlled trials in pregnant women included in this NDA submission. A non-clinical *in vivo* study demonstrated increased resorptions, decreased live fetuses, or reduced fetal weights observed at doses ≥0.10 mg/kg in pregnant rats administered intravenous doses of 0.01, 0.03, 0.10, and 0.15 mg/kg eribulin mesylate on gestation Days 8, 10, and 12. External or soft tissue anomalies were also noted at 0.15 mg/kg. The applicant concluded that eribulin mesylate causes embryofetal toxicity and teratogenicity at approximately half of the recommended dose based on body surface area.

A fertility study was not conducted with eribulin, but based on nonclinical findings in repeated-dose studies, male fertility may be compromised by eribulin. Testicular toxicity (hypocellularity of seminiferous epithelium with hypospermia/aspermia) was observed in rats administered 0.1 mg/kg eribulin (0.6 mg/m^2) weekly for 3 doses or 0.05 mg/kg (0.3 mg/m^2) weekly for 3 out of 5 weeks repeated for 6 cycles. Testicular toxicity was also observed in dogs administered 0.045 mg/kg (0.9 mg/m^2) weekly for 3 out of 5 weeks repeated for 6 cycles.

It is not known whether eribulin is excreted into human milk.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The applicant completed a dedicated drug-drug interaction trial with a strong CYP3A4 inhibitor (study 109). The effects of herbal products, diet, smoking and alcohol use on dose-exposure or response were not examined. There factors may not be important since eribulin has negligible liver metabolism.

2.4.2   Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in-vivo* drug-drug interactions?

No. Although eribulin is a substrate of CYP3A4 and Pgp, CYP3A4 is only responsible for its negligible metabolism. It is a weak inhibitor of Pgp.

See section 2.4.2.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes. Eribulin is a substrate of CYP3A4. However, eribulin undergoes limited metabolism based on the results of the *in vitro* metabolic stability study and the human mass balance trial.

It is unlikely that the metabolism of eribulin will be influenced by *CYP3A* genotype, since eribulin undergoes negligible metabolism in humans. The limited sequence variability identified in the three clinical pharmacology clinical trials in regards to *CYP3A* genotype, prohibited the exploration of a relationship between genotype and exposure.

An *in vitro* study indicated that the metabolism of eribulin (1-10 µM) was suppressed in the presence of 5 µM ketoconazole (DSDM-2004-009). A drug-drug interaction clinical trial demonstrated that eribulin exposure was similar when administered with or without ketoconazole, a strong CYP3A4 inhibitor (E7389-E044-109). See section 2.4.2.7.

The applicant's population PK/PD analysis indicates that eribulin clearance is not influenced by CYP3A inhibitors or inducers, as it appears that the clearance is similar between patients taking CYP3A4 inducers and inhibitors compared to patients not taking concomitant medications affecting CYP3A4 metabolism. Because the dose and timing of the administration of the inhibitors and inducers are not provided, the usefulness of this analysis is limited. Since eribulin undergoes negligible metabolism, it is unlikely that CYP3A inhibitors or inducers will yield clinically meaningful changes in systemic exposure as supported by the dedicated drug-drug interaction trial. Also see section 2.2.5.6 and 2.3.1.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

In vitro studies indicate that eribulin is unlikely to inhibit or induce the major cytochrome P450 enzymes. No clinical drug-drug interaction trials were conducted to determine the influence of eribulin on the systemic exposure of sensitive or narrow therapeutic substrates.

Inhibition: An *in vitro* study suggested eribulin is unlikely to inhibit major cytochrome P450 enzymes, including CYP1A2, CYP2C9, CYP2D6, CYP2E1 and CYP2C19 at clinically relevant concentrations (DMPK-2000-13).

Eribulin demonstrated concentration dependent reversible inhibition of CYP3A4 in pooled human liver microsomal preparations (**Table 13**). Eribulin (1, 5 or 10 µM) elicited minimal inhibitory effect on the metabolism of common CYP3A4 substrates carbamazepine, diazepam, paclitaxel, tamoxifen, midazolam, and terfenadine. The [I]/ K_i ratio indicates that the likelihood that eribulin can cause clinically relevant inhibition of CYP3A4 activity is remote.

Table 13. Reversible inhibition of CYP3A4 mediated metabolism by eribulin

Study Number	Substrate	K_i
DSD-2001-31	R-warfarin 10-hydroxylation	3 μM to 6 μM
	testosterone 6β-hydroxylation	5 μM to 17 μM
	nifedipine dehydroxylation	3 μM to 11 μM
DSDM-2004-009	testosterone 6β-hydroxylation	25 μM to 30 μM
	midazolam 1'-hydroxylation	10 μM to 15 μM
Source: non-clin sum report		

In vitro studies were not conducted to assess non-competitive or mechanism based inhibition.

Induction: The potential induction of human CYP1A and CYP3A by eribulin was determined using primary cultures of human hepatocytes from eight donors (DSD-2004-03). Eribulin at concentrations of 1 μM and 5 μM did not alter the activities of CYP1A or CYP3A and at concentrations of 0.05 μM to 5 μM did not alter the protein expression of these isozymes.

In primary human hepatocyte cultures from six donors (DSD-2000-46), eribulin (1, 5 or 10 μM) did not increase activity of CYP2C9-mediated tolbutamide 4-methylhydroxylation and CYP2C19-mediated *S*-mephenytoin 4'-hydroxylation. It also did not increase CYP2C9 or CYP2C19 protein expression levels.

Eribulin is not likely to induce these isozymes in humans, since the concentrations examined *in vitro* exceed the human plasma concentrations achieved at the proposed clinical dose. The potential for eribulin to induce CYP2A6, CYP2B6, and CYP2C8 was not evaluated.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Yes. Eribulin is a substrate and a weak inhibitor of Pgp. The effect of modulators of Pgp on the tissue distribution of eribulin in humans is unknown.

Substrate: The cell growth of drug sensitive and drug resistant human uterine cancer cells were grown for 96 hours in the presence and absence of eribulin and cell growth was assessed (study no. CAIVT0105 and CAIVT0106). The drug resistant (Pgp overexpressing) cells demonstrated marked resistance to eribulin compared to drug sensitive cells. The mean IC50 value for eribulin was 2 ± 0.05 nM in drug sensitive cells and was 5220 ± 1480 nM in drug resistant cells, and therefore, the drug resistant cells were 2670-fold less sensitive to eribulin than the drug sensitive cells. Verapamil, a Pgp inhibitor, was able to markedly increase the sensitivity of the drug resistant cells to eribulin, with a mean IC_{50} value of 78 ± 26 nM in drug resistant cells, a 427-fold less sensitive to eribulin than the drug sensitive cells in the presence of verapamil. The mean IC_{50} value in the drug sensitive cells is 125-fold lower than the maximal plasma concentrations (186 ± 67 ng/mL or 0.25 μM) reported for the proposed clinical dose, thus it is likely that eribulin will be transported by Pgp in humans. We recommend exploring the relationship between Pgp expression in tumors and clinical outcome and collect germline DNA for pharmacogenetic analyses of eribulin response and tolerability in the ongoing and future trials. For example, the applicant might consider whether genes of glutathione S-transferases are

associated with eribulin-induced neurotoxicity, especially the *GSTP* gene. Other genes involved in the cellular oxidative-stress pathway may also be worthy of investigation.

Inhibition: The influence of eribulin at concentrations ranging from 0 μM to 10 μM on the efflux ratio of digoxin in Caco-2 cell monolayers was determined (DDDA-2008-04). The IC_{50} of eribulin on Pgp activity was estimated to be greater than 10 μM; therefore, eribulin is likely a weak inhibitor of Pgp and further *in vivo* drug interaction trial is not warranted.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

No other metabolic or transporter pathways have been identified.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No, eribulin is recommended as a monotherapy.

2.4.2.7 Are there any *in-vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No. The dedicated drug-drug interaction trial demonstrated that eribulin's AUC was similar when administered with or without ketoconazole, a strong CYP3A4 inhibitor (study 109).

Twelve patients with advanced solid tumors were enrolled into a randomized, open-label, two-treatment, two-sequence, two-way crossover trial. Group one received eribulin on day 1 followed by eribulin plus ketoconazole on day 15 and ketoconazole alone on day 16. Group two received eribulin plus ketoconazole on Day 1, ketoconazole alone on Day 2 followed by eribulin on Day 15. The first cycle lasted 28 days. Eribulin was administered as an intravenous bolus dose of 1.4 mg/m^2 when given alone and 0.7 mg/m^2 when given with ketoconazole. Ketoconazole was administered orally at a dose of 200 mg daily once a day for 2 days. Blood sample were collected from Days 1 to 7 and Days 15 to 21. The dose normalized exposure was similar when eribulin was given with and without ketoconazole (ratio of geometric means 0.95, 90% CI 0.83, 1.12) (**Figure 17**).

Figure 17. Effect of ketoconazole on dose-normalized systemic exposure of eribulin
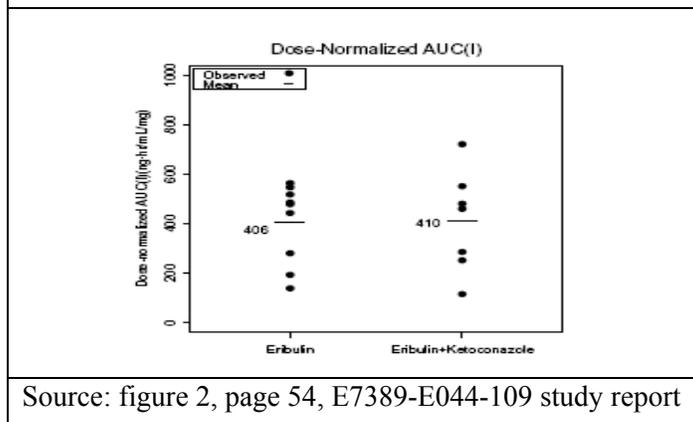
Source: figure 2, page 54, E7389-E044-109 study report

2.5   GENERAL BIOPHARMACEUTICS

2.5.1   Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable. Eribulin is intravenously administered.

2.5.2   What is the composition of the to-be-marketed formulation?

The applicant proposes to supply eribulin as a sterile, ready-to-use, clear, colorless aqueous solution for IV administration with each vial containing 1 mg of eribulin mesylate as a 0.5-mg/mL solution in ethanol:water (5:95).

2.5.3   What moieties should be assessed in bioequivalence studies?

Not applicable. Eribulin should be assessed in human plasma when conducting bioequivalence studies.

2.5.4   What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable for an intravenous drug product.

2.5.5   Has the applicant developed an appropriate dissolution method and specification that will assure *in-vivo* performance and quality of the product?

Not applicable for an intravenous drug product.

2.6   ANALYTICAL SECTION

2.6.1   How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The plasma concentrations and urinary excretion of eribulin measured as part of study NCI-5730 were determined using a LC-MS/MS assay method developed and validated in the   (b) (4)

A validated LC/MS-MS method was used to measure the plasma concentrations of eribulin in samples collected from study 101, 102 and 105 (report no. DSD-2004-36 and DSD-2003-28).

For the human mass balance trial, validated LC/MS-MS methods were used to measure eribulin in plasma, urine, feces, and whole blood (report no. E7389-E044-103\FIN\225) and total radioactivity in whole blood, urine and feces (report no. E7389-E044-103\FIN\245).

LC/MS-MS methods were used to measure the effects of the intrinsic and extrinsic factors on the PK of eribulin in study 108, 109 and 110 (report no. E7389\VAL\088).

2.6.2   Which metabolites have been selected for analysis and why?

Eribulin undergoes limited metabolism based on the *in vitro* metabolic stability analysis in human liver microsomal preparations and the human mass balance trial. No metabolites were selected for analysis. Eribulin is the only circulating compound that was measured.

2.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

The total plasma concentration of eribulin was measured in the clinical trials. No basis for this decision was provided, but protein binding of eribulin ranges from 46% to 65% for a concentration range of 100 ng/mL to 1000 ng/mL.

2.6.4 What bioanalytical methods are used to assess concentrations?

NCI-5730: The concentrations of eribulin in plasma and urine were determined using LC-MS/MS methods. The method utilized liquid-liquid extraction followed by reverse phase chromatography. The mass transition monitored for eribulin was from 730.5→712.5.

Study 101, 102 and 105: The concentrations of eribulin in plasma and urine were measured using LC-MS/MS on triple quadrupole mass spectrometers under positive ion mode. The method utilized liquid-liquid extraction followed by reverse phase chromatography. Eribulin was monitored at precursor ion *m/z*   (b) (4)   for plasma and urine, respectively.

Study 108, 109 and 110: Eribulin in plasma was quantified using a HPLC-ESI-MS/MS method on a quadrupole mass spectrometer under positive ion mode. The plasma clean-up procedure consisted of a liquid-liquid extraction and the compounds were separated by a reverse phase chromatography. The transition selected for eribulin was from *m/z* (b) (4) .

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

NCI-5730: The standard curve ranged from 0.1 ng/mL to 10 ng/mL. The reported Cmax appears to exceed the concentration of the highest calibrator included in the standard curve.

Linearity of the standard curve was determined using lease squares linear regression with 1/x weighting. Good linearity of the standard curve was achieved as indicated by a correlation coefficient of 0.999.

Study 101, 102 and 105: The quantifiable range of the assay was from 0.2 ng/mL to 100 ng/mL for plasma, and 0.5 ng/mL to 100 ng/mL for urine. Two levels of dilution were evaluated for both plasma and urine (1:1 and 1:10 dilutions or 1:50 dilutions, respectively). The concentration of the highest calibrator included in the standard curve allowing for a dilution adequately met the needs for the clinical trials.

A $1/x^2$ weighted linear regression of the peak area ratios was used to calculate slopes and intercepts. The concentration of eribulin in each sample was calculated from the regression equation of the standard curve. The coefficient of determination (r^2) for the regressions was at least 0.967 for plasma and at least 0.997 for urine.

Study 108, 109 and 110: The standard curve ranged from 0.206 ng/mL to 103 ng/mL. A dilution test sample (1:10) was prepared to determine the reliability of the method at concentration levels outside the calibration range (more than 100% of the ULQ concentration); the highest QC investigated was 500 ng/mL and was used to validate the accuracy and precision of the dilution methods. Based on the concentration of the highest QC following a dilution, the calibration range appears to have adequately met the needs for these clinical trials.

Linear regression of peak area versus concentration was weighted by $1/x^2$ to estimate eribulin concentrations. Correlation coefficients (r^2) of 0.9855 or better were obtained.

2.6.4.2 What are the lower and upper limits of quantification?

NCI-5730: The LLOQ was 0.1 ng/mL from a starting sample volume of 0.2 mL. The upper limit of quantification was 10 ng/mL.

Study 101, 102 and 105: The LLOQ was 0.2 ng/mL for plasma and 0.5 ng/mL for urine. The upper limit of quantification in plasma was 1000 ng/mL following a 1:10 dilution.

Study 108, 109 and 110: The LLOQ was 0.206 ng/mL for plasma. The upper limit of quantification in plasma was 500 ng/mL following a 1:10 dilution based on the target concentration of QC labeled VS (validation sample) > ULQ.

2.6.4.3 What are the accuracy, precision and selectivity at these limits?

NCI-5730: Intra- and inter-day precision and accuracy of the method were within ± 10% of target values over the entire range of the standard curve.

Study 101, 102 and 105: Intra- and inter-day precision and accuracy of the method were within ± 15% of target values over the entire range of the standard curve. The accuracy and precision of the diluted samples were within these acceptance criteria.

Six different lots of control plasma were evaluated and the peak area at the retention time of eribulin was compared with the lowest quantifiable standard. The lowest standard signal was at least five times greater than interfering peaks.

Study 108, 109 and 110: Intra- and inter-day precision and accuracy of the method were within ± 12% of target values over the entire range of the standard curve. The accuracy and precision of the diluted samples were within the acceptance criteria ± 15% of target values.

Selectivity was established by analysis of the LLOQ prepared from six different batches of control human plasma and the inclusion of double blank samples prepared from these batches. No interference from endogenous materials with areas > 20% of the LLOQ areas and no interference with areas > 5% of the internal standard area were observed.

2.6.4.4 What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

NCI-5730: The sample stability was not provided under conditions used in the trial.

Study 101, 102 and 105:

- Stock solution stability - Eribulin in MeOH stored at 4°C was compared to the response factors (in triplicate) of a 5000 ng/mL solution in a mixture of MeOH and H$_2$O (50:50), diluted from a greater than 29 month old stock (1 mg/mL), with one diluted from a freshly prepared stock (1 mg/mL) in MeOH. The mean percent difference of response was -1.5%.
- Freeze-thaw stability - The percent differences between concentrations after three freeze/thaw cycles and Day 0 for plasma ranged from -12.8 to 10.2%. The percent differences between concentrations following five freeze/thaw cycles and Day 0 for urine ranged from 2.7 to 14.4%.
- Room temperature stability - The mean percent difference between and nominal concentrations for plasma and urine after keeping the samples at room temperature for 4 hours, ranged from -14.8 to -7.1% and -5.5 to 1.4%,

- Whole blood stability - The mean percent differences between 1 and 3.5 hour samples versus time 0 samples concentrations for eribulin after being stored on wet ice ranged from 4.2 to 14.1%
- Re-injection reproducibility - The percent difference between the 60 hour reinjected concentrations and the first injection of 0.5, 50 and 100 ng/mL was -5.0%, 5.2%, and 13.1%, respectively, for plasma.
- Frozen stability - The mean percent differences between found and Day 0 concentrations for plasma and urine ranged from -15.0 to 11.8%, and -10.1 to 11.1%, respectively after a 651-day (plasma) and 176-day (urine) storage at -80°C.
- Autosampler stability - The percent difference between the 14-hour concentration and the first injection of 0.5, 50, and 100 ng/mL was -2.9%, 5.5% and 1.8%, respectively.

All levels were within the acceptable SOP limits for the validation of a bioanalytical method.

Study 108, 109 and 110:

- Stock solution stability, at least 6 h at ambient temperature in methanol
- Plasma freeze-thaw stability, at least 3 cycles
- Plasma stability, at least 24 h at ambient temperature
- In-process stability, at a maximum of 5 days at nominally 4°C as (b) (4)
- Processed stability, at least 5 days at ambient temperature as (b) (4)
- Re-injection reproducibility, at least 24 h at nominally 4°C
- Long-term stability, 38 months

2.6.4.5 What is the QC sample plan?

NCI-5730: QC samples containing eribulin in plasma at 0.15 and 8 ng/mL were prepared and five replicates of each QC were analyzed on each of the three validation days to determine inter-day precision and accuracy. Ten replicates from each the QC were analyzed on two different validation days to determine intra-day precision and accuracy.

Study 101, 102 and 105: QC samples were prepared by adding 50 μL of the appropriate QC solution to 450 μL of blank plasma or urine, resulting in 100, 50, 5, 1, 0.5 and 0.2 ng/mL of eribulin. Duplicates of each specified concentration level were prepared for each analytical run and for the interday validation. Five replicates of each specified concentration level were prepared for the intraday validation. The percent differences between the found and nominal concentrations for at least 2/3 of the QCs in each assay run were within 15% (20% for intra- and inter-day LLOQ).

Study 103, 108 and 109: The QC samples were prepared at concentrations of 0.2, 0.6, 5, 80 and 488 ng/mL. Six replicates of each QC in plasma were analyzed in at least three analytical runs to determine intra-assay performance.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. An <u>underline</u> indicates the content that was added to the proposed draft label by the agency and ~~strikethroughs~~ indicate content taken out by the agency from the proposed draft label.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
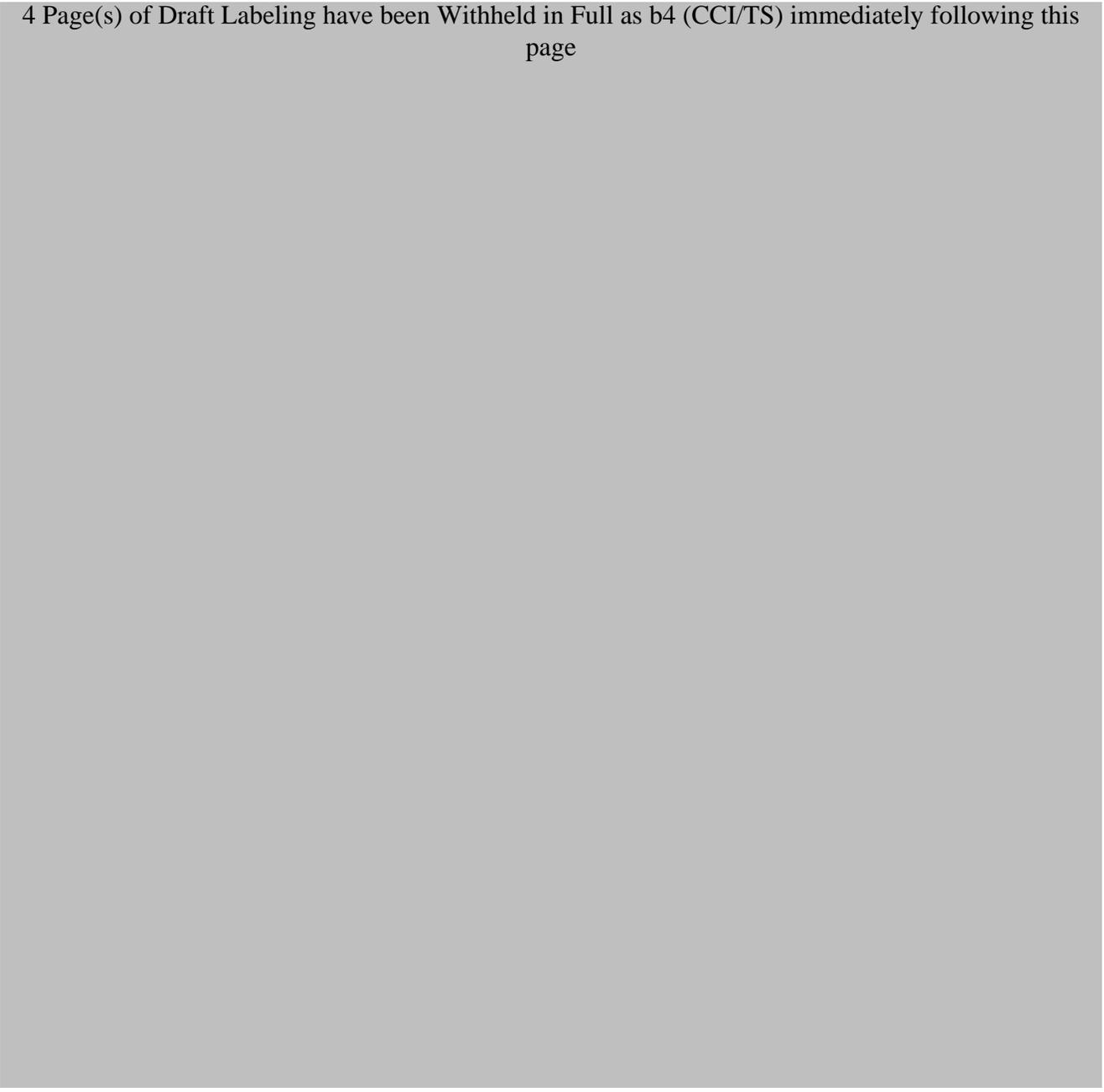
4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Application Number	201532
Submission Number (Date)	March 10, 2009
Compound (Dosing regimen)	Eribulin mesylate injection (1.4 mg/m2 IV bolus on days 1 and 8 of a 21 day cycle)
Clinical Division	DBOP
Primary PM Reviewer	Anshu Marathe, Ph.D.
Secondary PM Reviewer	Christine Garnett, Pharm.D.

1   SUMMARY OF FINDINGS

1.1   Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1   Is there evidence of exposure-response for effectiveness?

No, there is no evidence of exposure-response relationship for objective response rate, progression free survival and overall survival in patients with locally advanced or metastatic breast cancer in study 211 (Phase 2 trial). Exploratory exposure-efficacy analysis was conducted using data from study 211 because pharmacokinetic data was not collected in the pivotal trial (study 305). In study 211, sparse pharmacokinetic data was collected from 211 patients following 1.4 mg/m^2 dose of eribulin mesylate administered on days 1 and 8 of a 21 day cycle. The objective response rate by AUC quartile with 95% confidence intervals is shown in Figure 1. Given the confidence intervals, there appears to be no visual relationship between AUC and response rate. A time-to-event analysis was performed to assess the exposure-response relationship for effectiveness based on progression free survival and overall survival. The progression free survival and overall survival curves of patients in different AUC-quartile groups overlapped in Figure 1, thus indicating lack of exposure–response relationship. A likely reason for not observing exposure-response relationship is that this was a single arm trial with only one dose level that did not result in a wide range of exposures.

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B

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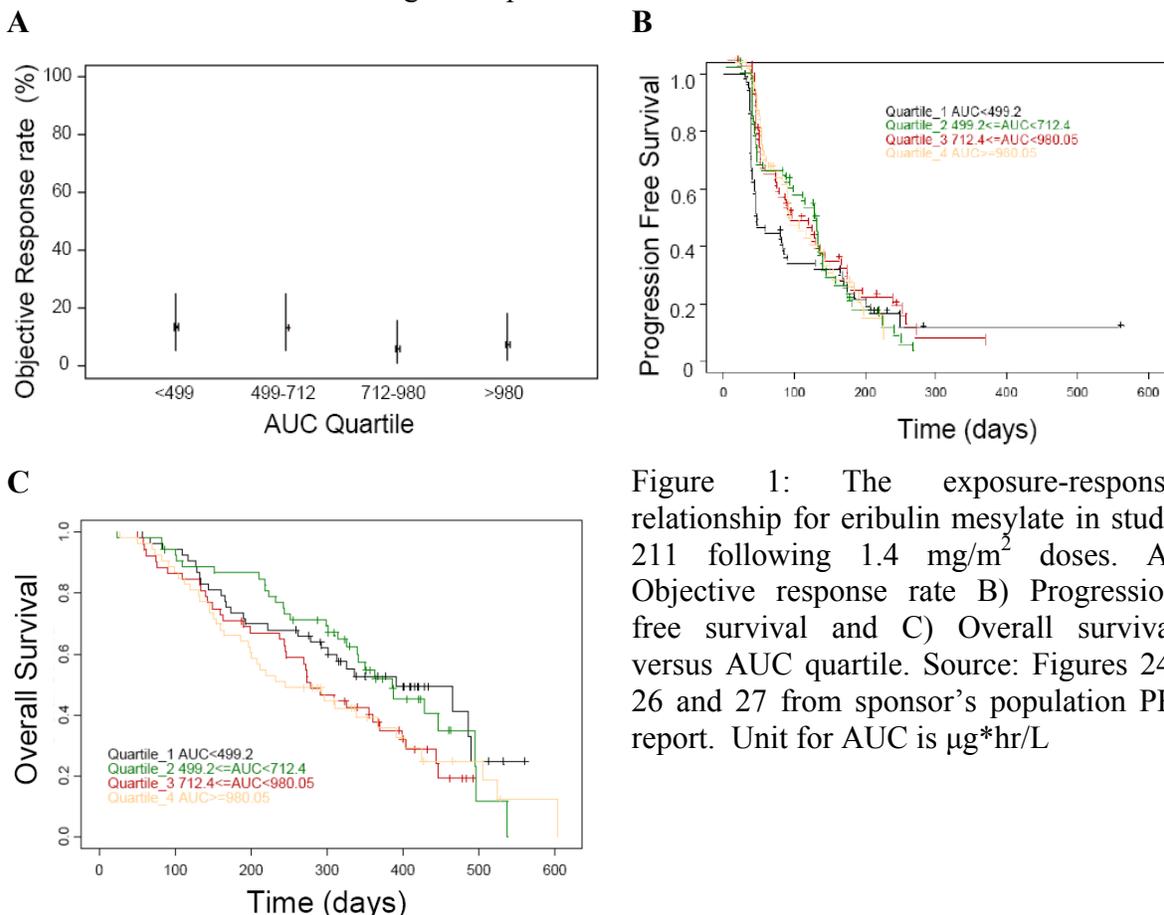
Figure 1: The exposure-response relationship for eribulin mesylate in study 211 following 1.4 mg/m^2 doses. A) Objective response rate B) Progression free survival and C) Overall survival versus AUC quartile. Source: Figures 24, 26 and 27 from sponsor's population PK report. Unit for AUC is μg*hr/L

1.1.2 Is there evidence of exposure-response for safety?

There is a trend for increased incidence of grade 3/4 neutropenia and grade 3/4 febrile neutropenia with increasing exposures in patients with locally advanced or metastatic breast cancer in study 211 following 1.4 mg/m^2 of eribulin mesylate (Figure 2). Binary logistic regression models were used to explore the relationship between exposure and AEs. Neutropenia and febrile neutropenia are the common treatment emergent AEs for eribulin mesylate. Data from 169 patients were used in the analysis. Patients with elevated levels of aspartate transaminase (AST) had higher sensitivity to experience neutropenia. At the same exposures, patients with elevated AST had higher incidence of grade 3/4 neutropenia (Figure 12).

A

B
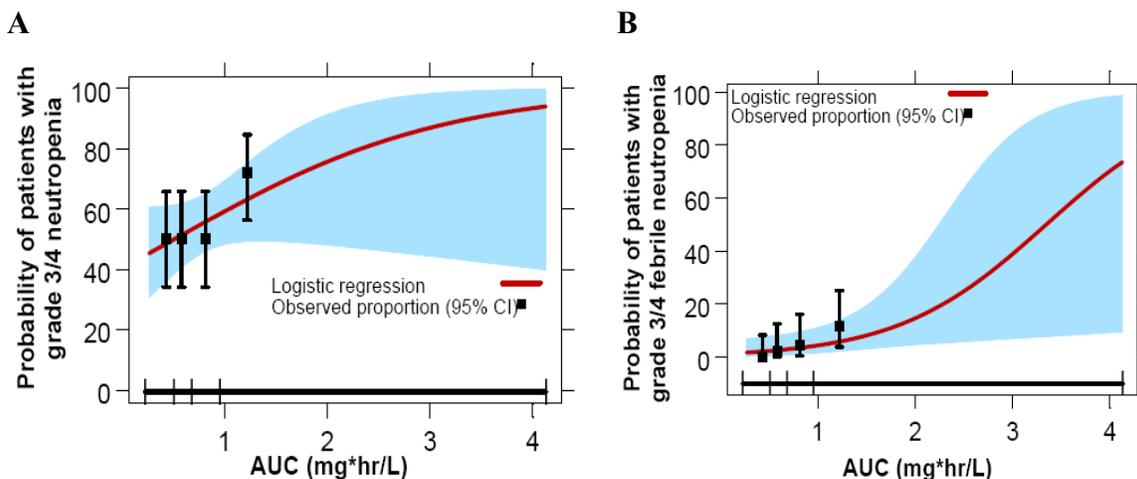
Figure 2: The probability of patients with various adverse events A) Grade 3/4 neutropenia B) Grade 3/4 febrile neutropenia in study 211 following 1.4 mg/m^2 doses. Solid black symbols represent the observed proportion of patients experiencing AEs in each AUC quartile. The vertical black bars represent the 95% confidence interval. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval of the prediction. The exposure range in each AUC quartile is denoted by the horizontal black line.

1.1.3 Is the proposed dose adjustment for patients with adverse events appropriate?

Based on exposure-response relationship conducted using data from study 211, dose reduction from 1.4 to 0.7 mg/m^2 will not cause significant reduction in grade 3/4 neutropenic events. Sponsor has proposed to reduce dose from 1.4 to 1.1 mg/m^2 if patients experience grade 3 or 4 neutropenia. Further dose reduction to 0.7 mg/m^2 is proposed if grade 3 or 4 neutropenia re-occur (Table 6). The logistic regression model shows that decreasing the dose from 1.4 to 1.1 mg/m^2 would reduce the probability of patients experiencing grade 3/4 neutropenia from 55% to 52%. Dose reduction to 0.7 mg/m^2 would reduce the probability of patients experiencing grade 3/4 neutropenia to 48%. Thus a dose reduction of 50% to 0.7 mg/m^2 will reduce the risk by 7% (Table 9). This analysis is limited by data from a phase 2 trial because pharmacokinetic data was not collected in the pivotal trial (study 305).

In study 305, eribulin related grade 3 neutropenia and grade 4 neutropenia occurred in 21% and 24% of the patients. In the eribulin arm, 23% of the patients had dose delays, dose reductions or discontinued treatment due to neutropenia. There were 18% of the patients who received G-CSF in the eribulin arm. As exposure-response analysis shows that dose reduction alone will not reduce the risk of neutropenia significantly, it is likely that dose delays and G-CSF administration might be needed as part of the clinical management for this adverse event.

According to Dr. Donoghue (Clinical Reviewer), neutropenia was managed reasonably well in the pivotal trial.

1.1.4 Does eribulin prolong QTc interval?

Yes, a delayed prolongation in QTc interval was observed upon administration of 1.4 mg/m^2 of eribulin on days 1 and 8 of a 21 day cycle in a dedicated study conducted in patients with advanced solid tumor. The maximum mean QTcF change from baseline (95% upper confidence interval) was 11.3 (18.2) ms on day 8 (See the QT-IRT review for more details). The QTc prolongation is not concentration-dependent and there appeared to be no increase in QTcF with increasing drug concentrations (Figure 3).

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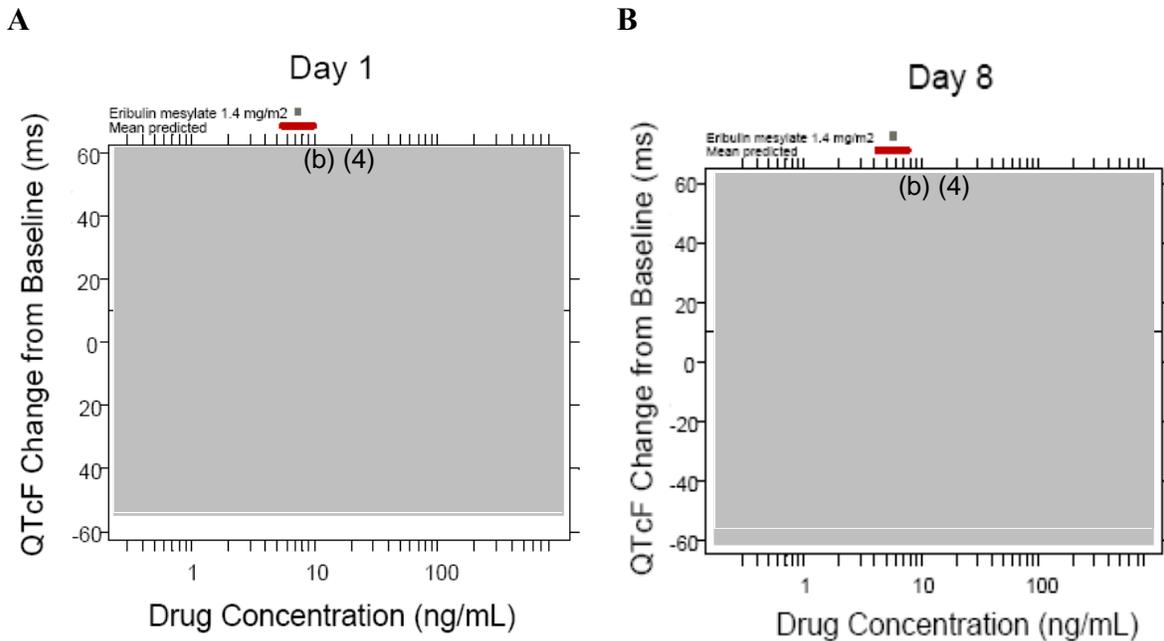
Figure 3: Scatter plot of QTcF change from baseline (ΔQTcF) versus eribulin mesylate concentration on A) day 1 and B) day 8 of the dosing cycle. Solid red line represents the mean predicted ΔQTcF. Black line represents a ΔQTcF of 10 ms.

1.1.5 Is the proposed dose of 1.4 mg/m^2 adequate to obtain similar exposures across patients with renal impairment?

A slight trend is observed between creatinine clearance (CL$_{CR}$) and clearance (CL) for patients with mild and moderate renal impairment (Figure 4). The median CL for subjects with moderate renal impairment was lower (1.65 L/hr) compared to normal subjects (3.32 L/hr). Thus, a 2-fold increase in median dose-normalized AUC is observed for subjects with moderate renal impairment. Data from 269 patients were used in the analysis. Non compartmental analysis of PK data also showed similar trend (See Dr. Stacy Shord's Clinical Pharmacology Review for more details). No dose adjustments are necessary for mild renal impairment, a lower starting dose is recommended for patients with moderate and severe renal impairment. The increase in exposure in severe renal impaired patients needs to be explored by the sponsor. A PK trial in patients with severe renal impairment is recommended as a post-marketing requirement (see Executive Summary of Clinical Pharmacology Review).

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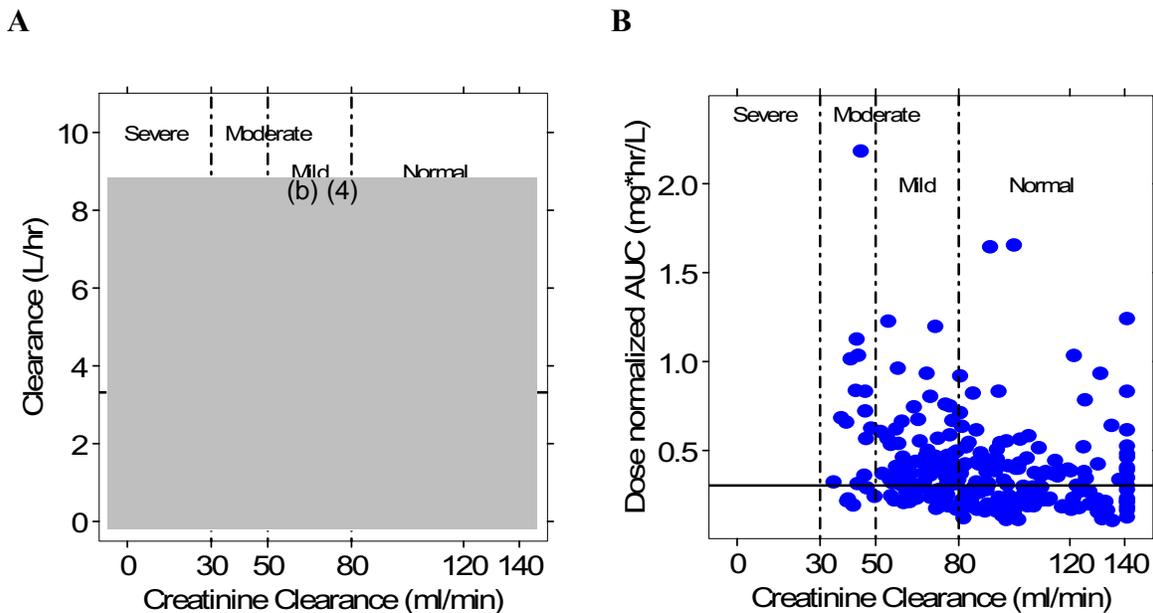
Figure 4: A) Clearance vs. Creatinine Clearance and B) Dose normalized AUC vs. Creatinine Clearance. The horizontal black line represents the median value of CL and AUC in subjects with normal renal function.

1.2 Recommendations

Division of Pharmacometrics finds the NDA acceptable from a clinical pharmacology perspective and has the following recommendations for the sponsor.

- For future development programs, the sponsor should collect sparse pharmacokinetic data from all subjects. The purpose is to develop exposure response relationship for efficacy and safety endpoints to support proposed dosing recommendations and dose adjustments.

1.3 Label Statements

The following are the labeling recommendations relevant to clinical pharmacology for NDA 22468. The ~~red strikeout font~~ is used to show the proposed text to be deleted and <u>underline blue font</u> to show text to be included or comments communicated to the sponsor.

(b) (4)

Reviewer's comments:

- *The statement based on population analysis in section 7.1 of the label is deleted because in case of CYP3A4 inhibitors, sponsor conducted a dedicated study and the results from the study is recommended in the label (see Detailed Labeling Recommendations of the Clinical Pharmacology Review). The overall conclusion from the dedicated study and POPPK analysis are in agreement. The statement regarding CYP3A4* (b) (4) *.*

- *The statement regarding renal impairment in section 8.6 of the label is deleted because* (b) (4) *A lower starting dose is recommended for patients with moderate and severe renal impairment (see Detailed Labeling Recommendations of the Clinical Pharmacology Review). A PK trial in patients with severe renal impairment is recommended as a post-*

marketing requirement (see Executive Summary in the Clinical Pharmacology Review).

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK Analysis

Sponsor performed population PK modeling utilizing data from eight studies that evaluated eribulin mesylate in advanced cancer patients. Primary objective of the population PK analysis was to identify patient factors (age, race, gender, renal function, concomitant administration of CYP3A4 inhibitors/ inducers etc.) that may affect PK and therefore may require dose adjustment. The performance of the final PK model was evaluated.

2.1.1 Methods

PK Data from a total of 269 patients (2729 observations) from seven Phase 1 studies and one Phase 2 study was utilized for the development of the population PK model. Description of the studies with other relevant information is provided in Table 1.

Table 1: Studies Used for the Population PK Model

Study No.	Doses studied (mg/m^2)	Indication	Sample collection
E7389-A001-101	0.25, 0.5, 0.7, 1 and 1.4 mg/m^2 on days 1, 8 and 15 of 21 day cycle	Advanced solid tumors	Rich
E7389-A001-102	0.25, 0.5, 1.0, 2.0, 2.8 and 4.0 mg/m^2 on day 1 of 21 day cycle	Advanced solid tumors	Rich
E7389-A001-103	2 mg dose of ^{14}C-eribulin	Advanced solid tumors	Rich
E7389-A001-105	0.7, 1.0, 1.4 and 2.0 mg/m^2 on days 1 and 8	Solid tumors	Rich
E7389-A001-108	1.4 mg/m^2	Advanced solid tumors with normal or reduced hepatic function	Rich
E7389-A001-109	1.4 mg/m^2	Advanced solid tumors	Rich
E7389-A001-110	1.4 mg/m^2 on days 1 and 8 of a 21 day cycle	Advanced solid tumors	Rich
E7389-G000-211	1.4 mg/m^2 on days 1 and 8 of a 21 day cycle	Metastatic or locally advanced breast cancer	Sparse

PK data were then fitted using Nonmem Version VI Level 2 (b) (4)).
Model building and covariate assessments were conducted using standard methods. The final model for the PK database was evaluated for performance using several tests, including evaluation of an internal validation database, nonparametric bootstrapping, and visual predictive check (VPC) evaluation.

2.1.2 Conclusions

- The population PK for eribulin mesylate was described by a three compartment model with linear elimination.

- The final model included WT as a covariate on CL, V1, V2, V3, Q2 and Q3. Albumin, alkaline phosphatase and bilirubin were included as a covariate on CL and dose on Q2.

- The effects of age, gender, creatinine clearance, race and co-administration of CYP3A4 inducers and inhibitors were not identified as being important predictors of clearance.

Parameter estimates for fixed effect and random effects with standard errors are presented in Table 10 in the Appendix (section 4). Basic goodness of fit plots from the sponsor's final model is presented in Figure 13 in the Appendix.

Reviewer's comments on Sponsor's Population PK Analysis:

- *Sponsor's population PK analysis is generally adequate and acceptable.*
- *The covariates that were identified in the final model are likely not to be significant as the inclusion of all the covariates resulted in the reduction in the objective function value (OFV) by 118 from the sponsor's base model using allometric function to the final model. The inter-individual variability on clearance (CL) was reduced from 54% to 46% and the inter-occasion variability decreased from 15.3% to 13.9%.*
- *No clear trends were identified between the PK parameters obtained from the model and age/race/gender in reviewer's analysis (see section 3.3).*
- *No significant effect of CYP3A4 inhibitors or inducers was identified on eribulin mesylate exposures. The POP PK results obtained for CYP3A4 inhibitors supports the findings of a dedicated study where similar exposures were observed in subjects when eirbulin was administered in combination with ketoconazole as compared to eribulin administered alone. A dedicated study was not conducted for CYP3A4 inducers and lack of drug-drug interaction with inducers is not adequately supported by POP PK analysis because the dose and the timings for the administration of inducers are unclear. Based on in vitro data, however, drug-drug interactions are not expected.*
- *A slight trend was observed between clearance (CL) and creatinine clearance (CL_{CR}) for patients with moderate and mild renal impairment (see reviewer's analysis), suggesting that a stronger relation is likely to exist between CL and CL_{CR} for patients with severe renal impairment.*

2.2 Exposure-Response Analysis for Effectiveness

The objective was to conduct exploratory graphical assessment of the possible relationships between eribulin exposure and measures of clinical outcome for efficacy.

2.2.1 Methods

Data from 211 patients with PK information from study 211 were utilized for a graphical assessment of exposure-response relationship for objective response rate, progression free survival and overall survival. Box plots and Kaplan-Meier curves were used for the analysis. The response rate was defined as the proportion of subjects with complete response and partial response. Only AUC arising from the first cycle was used. The sponsor's data for objective response rate, overall survival and PFS in study 211, consisting of 269 patients in the eligible population is provided in Table 2, Table 3 and Table 4.

Table 2: Summary of Objective Response Rate

	Investigator N=269	Independent Reviewer[a] N=269
CR, n (%)	1 (0.4%)	0 (0.0%)
PR, n (%)	37 (13.8%)	25 (9.3%)
SD, n (%)	132 (49.1%)	125 (46.5%)
PD, n (%)	94 (34.9%)	116 (43.1%)
Not evaluable, n (%)	5 (1.9%)	3 (1.1%)
Overall response (CR+PR), n (%)	38 (14.1%)	25 (9.3%)
95% CI[b]	[10.2, 18.9]	[6.1, 13.4]
p-value[c]	0.656	0.996
Disease control rate (CR+PR+SD), n (%)	170 (63.2%)	150 (55.8%)
95% CI[b]	[57.1, 69.0]	[49.6, 61.8]
Clinical benefit rate (CR+PR+SD ≥ 6 months), n (%)	53 (19.7%)	46 (17.1%)
95% CI[b]	[15.1, 25.0]	[12.8, 22.1]

(Source: Sponsor's Report for Study 211, Table 11)

Table 3: Kaplan-Meier Analysis of Overall Survival

	Total Patients (N = 269)
Number of patients who died	170
Number of patients censored	99
Min, max	19, 604
Median survival (days)	315
95% CI for median	[279, 350]
6-month survival rate (%)	72.3
95% CI	[66.9, 77.6]

(Source: Sponsor's Report for Study 211, Table 14)

Table 4: Kaplan-Meier Analysis of Progression Free Survival

Kaplan-Meier Estimates	Investigator N=269	Independent Reviewer[2] N=269
Progression-Free Survival (PFS) (days)		
Number of patients who progressed or died[2]	213	220
Number of patients censored	56	49
Min-max [1]	1+ - 397	1+ - 397+
Median	87	79
95% CI for median	[79, 116]	[64, 92]
12-week progression-free survival rate (%)	53.0	45.9
95% CI	[46.8, 59.1]	[39.8, 52.1]
6-month progression-free survival rate (%)	20.0	15.6
95% CI	[14.6, 25.3]	[10.7, 20.5]

(Source: Sponsor's Report for Study 211, Table 13)

2.2.2 Conclusions

- No visual trends could be established between the first cycle of eribulin exposure and measures of response (objective response rate, progression free survival and overall survival) to treatment (see Figure 1).

Reviewer's comments on Sponsor's Exposure-Response Analysis for Effectiveness: The sponsor's conclusion of no visual correlation between exposure and response in study 211 is acceptable. However, a likely reason for not observing exposure-response relationship is that this was a single arm trial with only one dose level that did not result in a wide range of exposures (see reviewer' comments in 1.1.1). This is an exploratory analysis because data from the phase 2 study was utilized as PK information was not available from the pivotal trial (study 305).

2.3 Exposure-Response Analysis for Safety

The objective of this analysis was to link drug exposures to probability of adverse events and to identify patient factors that may affect the probability of experiencing an AE and therefore may require dose adjustment.

2.3.1 Methods

Data from study 211 were used for the PK/AE evaluation. The safety population in the study constituted of 291 patients. The final database used for model building and evaluation consisted of 1050 observed adverse event records from 211 patients who had individual pharmacokinetic parameter estimates. Graphical assessments of the relationships between measures of eribulin exposure (Dose,
Cmax and AUC) and adverse events (neuropathy and neutropenia) were conducted. Following graphical assessments, ordered categorical logistical regression analysis was used to evaluate the probability of neuropathy and neutropenia.

2.3.2 Conclusions

- The probability of patients experiencing Grade 4 neutropenia is related to eribulin AUC and AST. Patients with high AST (potentially indicating poor hepatic function) appear to be more likely to experience Grade 4 neutropenia than patients with normal AST levels as shown in Figure 5 .
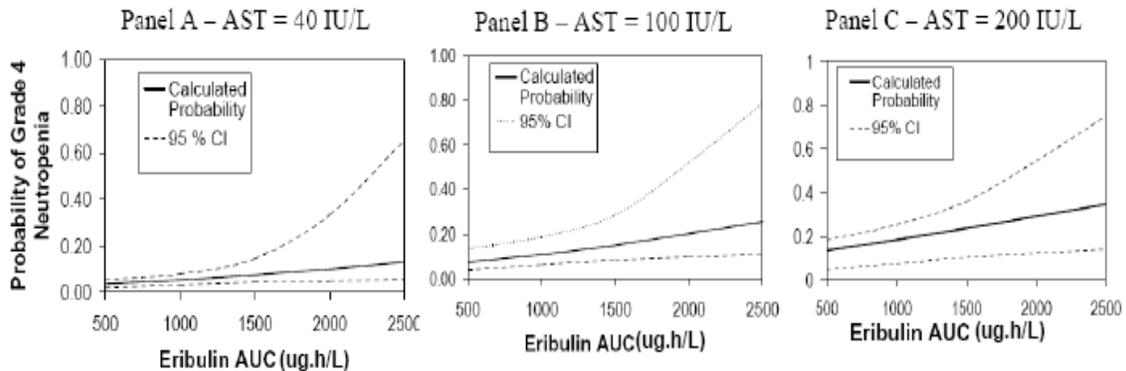

Figure 5: Calculated probability of patients experiencing grade 4 neutropenia for different levels of AST

(Source: Sponsor's Population PK Report, Figure 23, Pg 63)

- The probability of patients experiencing Grade 3 neuropathy was related to eribulin exposure and the number of treatment cycles administered (Figure 6). Because the probability of neuropathy is low at eribulin exposures that are likely to be experienced in the clinic, this finding has little clinical relevance.
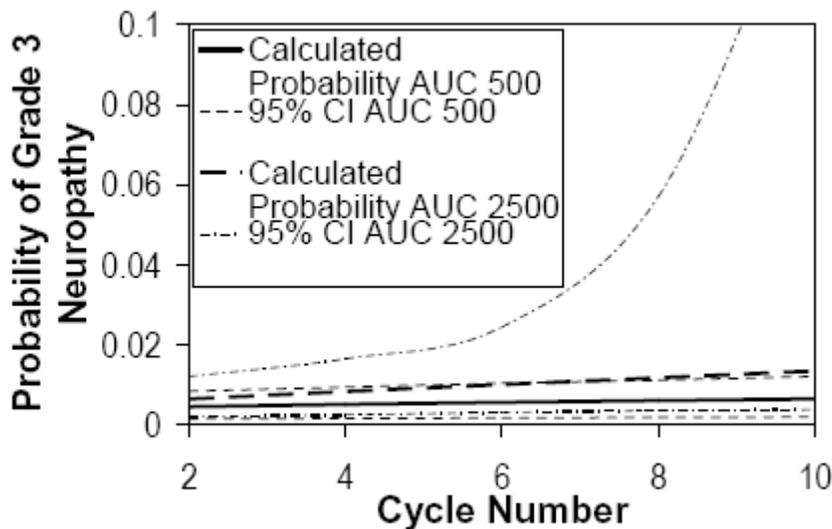
Figure 6: Calculated probability of patients experiencing grade 3 neuropathy at different exposure levels

(Source: Sponsor's Population PK Report, Figure 21, Pg 59)

- The model shows that a dose reduction from 1.4 mg/m^2 to 0.7 mg/m^2 provides similar exposures in patients with moderate hepatic impairment compared to normal subjects. With the recommended dose of 0.7 mg/m^2 the probability of Grade 4 neutropenia would be substantially lowered for patients with moderate hepatic impairment. Because of the elevated AST in patients with moderate hepatic impairment, these probabilities would still be somewhat higher than would be seen in patients with normal hepatic function.

A   **B**
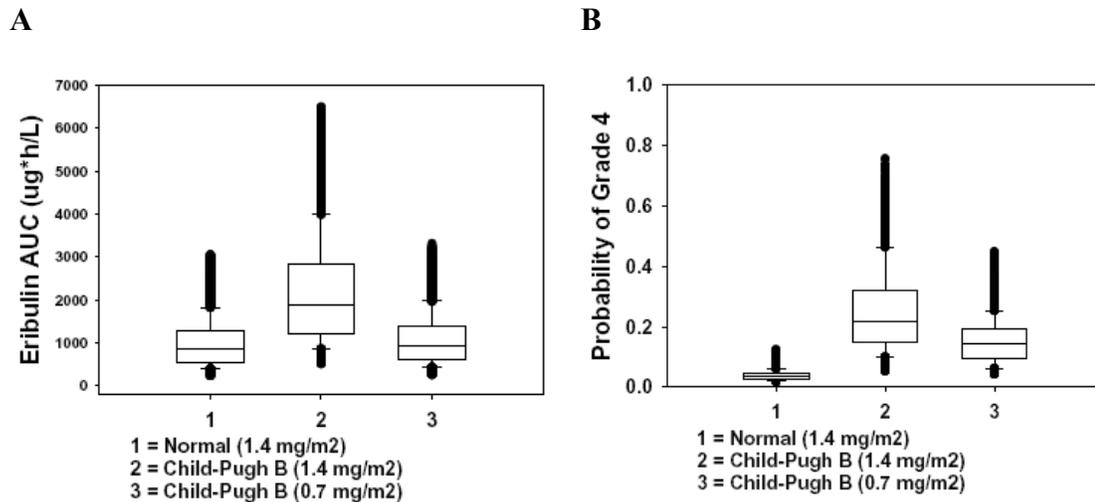
Figure 7: Calculated A) Eribulin AUC and B) Probability of experiencing grade 4 neutropenia for patients with normal and moderately impaired hepatic function

Reviewer's comments on Sponsor's Exposure-Response Analysis for Safety:

- *The sponsor's conclusion that the probability of grade 4 neutropenia is related to drug exposure and AST is acceptable. A trend for increase in grade 4 neutropenia with exposure is shown in reviewer's analysis in Figure 11. Also Figure 12 in reviewer's analysis shows that patients with elevated AST have higher probability of experiencing grade 3/4 neutropenia.*
- *The sponsor's conclusion that the probability of grade 3 neuropathy is related to exposure and number of cycles administered is likely not to be significant because the estimated shrinkage of the model was fairly high (46.2%). Reviewer's analysis showed no effect of AUC on the probability of experiencing grade 2/3/4 neuropathy (Figure 11).*
- *The sponsor's conclusion regarding dose reduction in patients with moderate hepatic impairment is reasonable because reducing the dose to 0.7 mg/m^2 results in similar exposures as healthy subjects. The probability of grade 4 neutropenia is reduced without compromising on the effectiveness of eribulin.*

3   RESULTS OF REVIEWER'S ANALYSIS

3.1   Objectives

The reviewer's analysis objectives are:

1. To determine the exposure-response relationship for safety endpoints of eribulin mesylate.

2. To use the results of objective (1) to establish whether proposed dose adjustment for adverse events is adequate.

3. To explore whether the proposed dose of 1.4 mg/m^2 is adequate to obtain similar exposures across patients.

3.2   Methods

3.2.1   Data Sets

Data sets used are summarized in Table 5.

Table 5: Analysis Data Sets.

Study Number	Name	Link to EDR
Phase 1 E7389-A001-101 E7389-A001-102 E7389-A001-103 E7389-A001-105 E7389-A001-108 E7389-A001-109 E7389-A001-110 Phase 2 E7389-G000-211	pkmodall.xpt	\\Cdsesub1\evsprod\NDA201532\0000\m5\datasets\pop-pk\analysis
E7389-G000-211	aeterm.xpt keyfile.xpt	\\Cdsesub1\evsprod\NDA201532\0000\m5\datasets\e7389-g000-211\analysis

3.2.2   Software

SAS, R, S-PLUS, NONMEM were used for the reviewer's analyses.

3.3 Results

3.3.1 Population Pharmacokinetic Analysis

Age, race and gender do not significantly affect the pharmacokinetics of eribulin. Figure 8 shows that the inter-individual variability in clearance cannot be explained by age. Boxplot of the inter-individual variability on clearance show that there is no systematic trend between males and females as evidenced by a median of zero (Figure 8). Similarly, no systematic trend is observed for race.
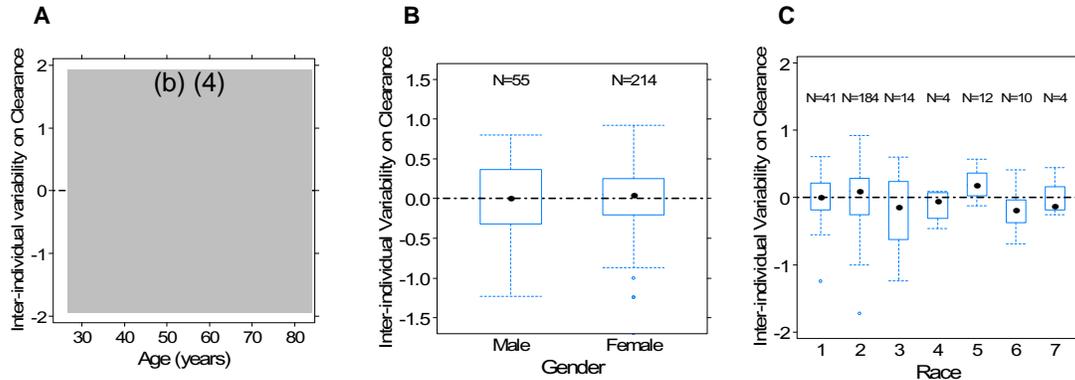

Figure 8: Inter-individual variability on clearance vs. A) Age B) Gender and C) Race. 1=Missing, 2=White, 3=Black, 4=Asian (non-Japanese), 5=Japanese, 6=Hispanic, 7=Other

CYP3A4 inhibitors or inducers may not affect the pharmacokinetics of eribulin. Boxplot of the inter-individual variability on clearance show that there is no systematic trend between subjects taking inhibitors/inducers compared to subjects not taking them (Figure 8). Lack of drug-drug interaction with inducers is not adequately supported by POP PK analysis because the dose and the timings for the administration of inducers are unclear. A dedicated study for CYP3A4 inducers was not conducted by the sponsor.
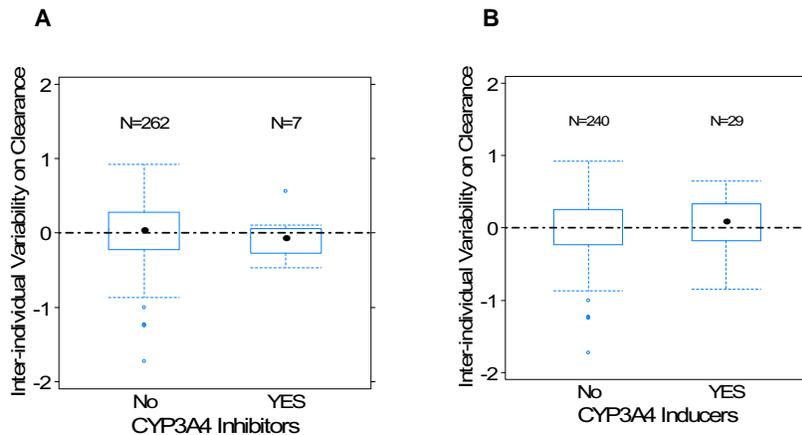

Figure 9: Inter-individual variability on clearance vs. concomitant use of A) CYP3A4 inhibitors and B) CYP3A4 inducers

A slight trend is observed between inter-individual variability on clearance and creatinine clearance (CL_{CR}) for patients with mild and moderate renal impairment (Figure 9A). Figure 9B shows that the median CL for subjects with moderate renal impairment was lower (1.6 L/hr) compared to normal subjects (3.3 L/hr). Thus, a 2-fold increase in median dose-normalized AUC is observed for subjects with moderate renal impairment. This implies that a stronger relation is likely to exist for patients with severe renal impairment and thus needs to be further explored by the sponsor
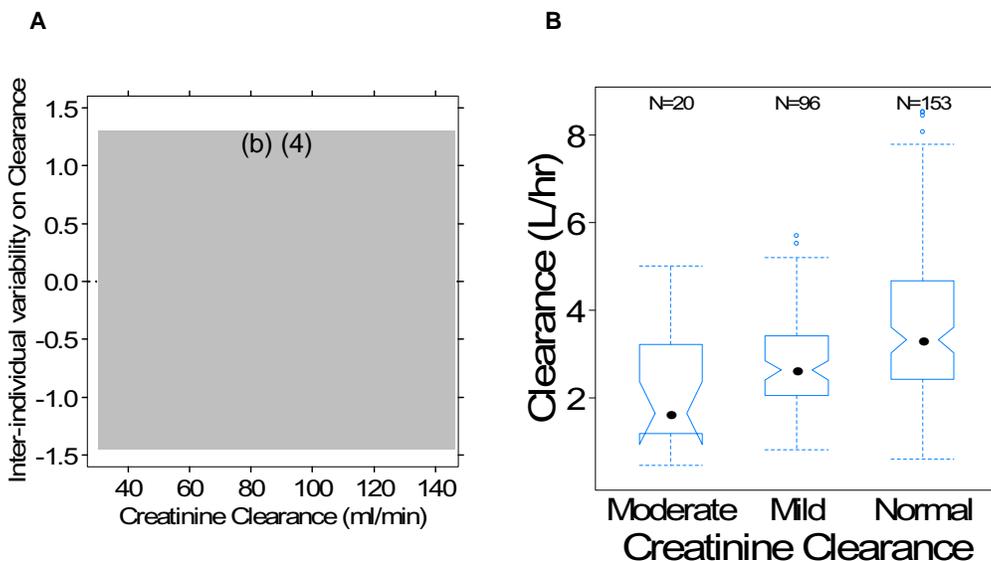
Figure 10: A) Inter-individual variability on clearance and B) Clearance vs. Creatinine Clearance

3.3.2   Exposure-Response Analysis for Safety

The common treatment related adverse events experienced by patients in the pivotal study (study 305) were fatigue, neutropenia, alopecia, nausea and peripheral neuropathy. Dose modifications for grade 3/4 neutropenia, grade 3/4 febrile neutropenia and for any other toxicity grade 3 or higher has been recommended by the sponsor and is provided in Table 6. The sponsor proposes that if grade 3 or higher toxicity occurs, treatment should be delayed to allow recovery and then should be followed by dose reduction. Table 7 shows the proportion of patients experiencing neutropenia, febrile neutropenia and peripheral neuropathy in study 211. As pharmacokinetic data was unavailable in the pivotal study, data from study 211 was utilized to perform exposure response analysis for safety.

(b) (4)

(Source: Sponsor's Label)

Table 7: Adverse Events Occurring in ≥ 10% of Patients in Study 211.

AE	Eribulin Mesylate (N=291)		
	Grade 3 n (%)	**Grade 4 n (%)**	**Total n (%)**
Neutropenia	64 (22)	93 (32)	174 (60)
Febrile Neutropenia	8 (3)	8 (3)	16 (6)
AE	**Grade 3/4 n (%)**		**Total n (%)**
Peripheral Neuropathy	16 (6)		70 (24)

(Source: Sponsor's Study 211 Report, Table 25 and section 14)

Binary logistic regression models were used to explore the relationship between exposure and treatment emergent AE's specifically neutropenia, febrile neutropenia, and peripheral neuropathy.

A   B
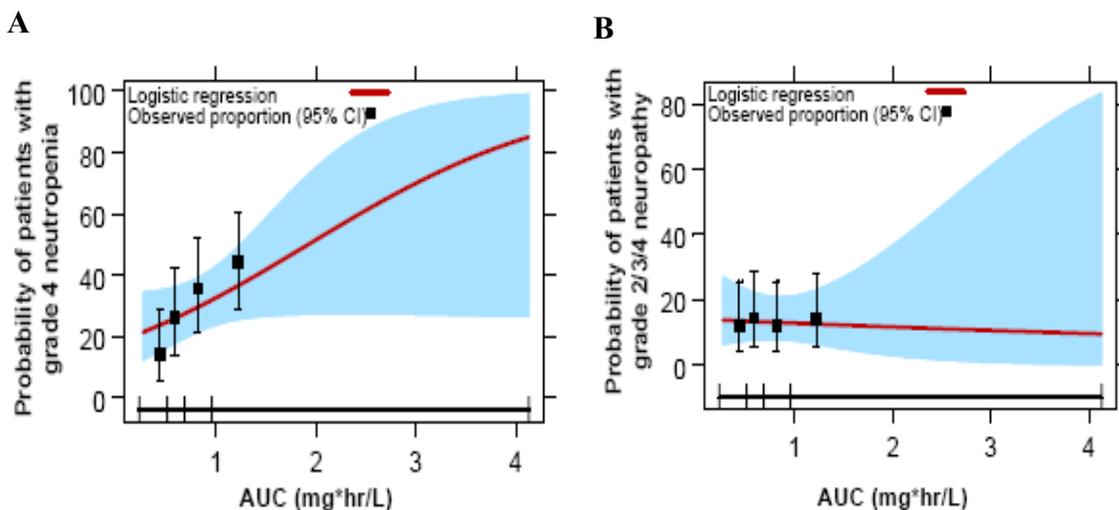
Figure 11: The probability of patients with various adverse events A) Grade 4 neutropenia and D) Grade 2/3/4 neuropathy-AUC profile for eribulin. Solid black symbols represent the observed percentage of patients experiencing AEs in each AUC quartile. The black bars represent the 95% confidence interval. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval. The exposure range in each AUC quartile is denoted by the horizontal black line.

Table 8: Reviewer's Logistic Regression Analysis Parameter Estimates.

Adverse Event	Intercept Estimate	Slope Estimate	P-value	Odds Ratio (95% CI)	N
Grade 3/4 neutropenia	-0.390	0.76	.045	2.14 (1.02 - 4.51)	169
Grade 3/4 febrile neutropenia	-4.38	1.31	.003	3.70 (1.57 - 8.76)	169
Grade 4 neutropenia	-1.51	0.78	0.02	2.19 (1.13 - 4.24)	169
Grade 2/3/4 neuropathy	-1.81	-0.109	0.817	0.897 (0.359 – 2.25)	169

There is a trend for increased incidence of grade 3/4 neutropenia, grade 3/4 febrile neutropenia and grade 4 neutropenia with increasing exposures (Figure 2 and Figure 11). The p-values were less than 0.05 and the odds ratio excluded 1 (Table 8). No effect of AUC was observed on the probability of patients with grade 2/3/4 neuropathy (p=0.817). The probability of patients with grade 3/4 neutropenia and grade 3/4 febrile neutropenia for median AUC values (exposures) obtained after administration of 1.4, 1.1 and 0.7 mg/m^2 doses are shown in Table 9. The probability of patients experiencing grade 3/4 neutropenia and grade 3/4 febrile neutropenia reduces from 55.2% to 52% and 3.4% to 2.8 respectively upon dose reduction. It is important to note that the intersubject variability in clearance (46%) is larger than the proposed dose reduction from 1.4 – 1.1

mg/m^2 (20%). Dose reduction to 0.7 mg/m^2 would reduce the probability of patients experiencing grade 3/4 neutropenia to 47.7%. Thus a dose reduction of 50% to 0.7 mg/m^2 will reduce the risk by 7%. This analysis is limited by data from a phase 2 trial because pharmacokinetic data was not collected in the pivotal trial (study 305).

In study 305, eribulin related grade 3 neutropenia and grade 4 neutropenia occurred in 21% and 24% of the patients. In the eribulin arm, 23% of the patients had dose delays, dose reductions or discontinued treatment due to neutropenia. There were 18% of the patients who received G-CSF in the eribulin arm. As exposure-response analysis shows that dose reduction alone will not reduce the risk of neutropenia significantly, it is likely that dose delays and G-CSF administration might be needed as part of the clinical management for this adverse event.

According to Dr. Donoghue (Clinical Reviewer), neutropenia was managed reasonably well in the pivotal trial.

Table 9: Reviewer's Logistic Regression Results for Dose Reduction

Dose (mg/m^2)	Median AUC (mg*hr/L)	Probability of patients with Grade 3/4 Neutropenia (%)	Probability of patients with Grade 3/4 Febrile Neutropenia (%)	Probability of patients with Grade 4 Neutropenia (%)
1.4	0.786	55.2	3.39	29.1
1.1	0.618	52	2.74	26.4
0.7	0.393	47.7	2.06	23.1

Patients with elevated levels of aspartate transaminase (AST) had higher sensitivity to experience neutropenia. Figure 12 shows that at the same exposures, patients with elevated AST had higher incidence of grade 3/4 neutropenia
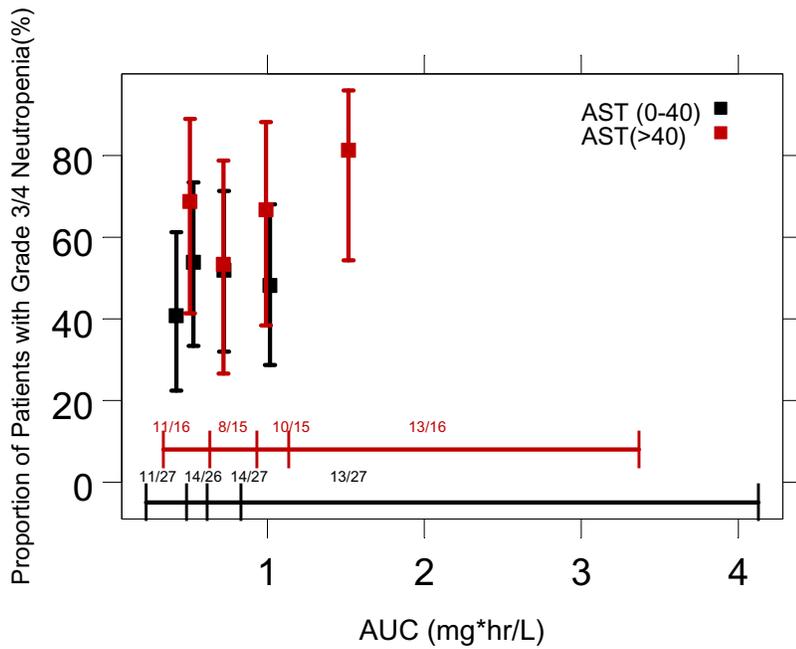
Figure 12: The proportion of patients with grade 3/4 neutropenia vs. AUC for different levels of AST. Symbols represent the observed percentage of patients experiencing AEs in each AUC quartile. The vertical black bars represent the 95% confidence interval. The exposure range in each AUC quartile is denoted by the horizontal line.

4 APPENDIX A: SPONSOR'S POPULATION PK ANALYSIS

Table 10: Sponsor's Final PK Model parameters for Eribulin

Parameter (Units)		Population Mean (SE*)	%CV Inter-Individual Variance (SE*)	%CV Inter-Occasion Variance (SE*)
CL (L/h)	Θ_1	2.48 (10.7)	45.61 (13.5)	13.89 (31.6)
Weight	...	0.75 FIX		
Albumin	Θ_7	1.02 (17.3)		
AlkPhos	Θ_8	-0.142 (35.0)		
Bilirubin	Θ_9	-0.203 (28.3)		
VC (L)	Θ_2	4.08 (4.1)	42.31 (28.0)	NE
Weight	...	1 FIX		
Q2 (L/h)	Θ_3	6.22 (31.7)	NE	NE
Weight	...	0.75 FIX		
Dose	Θ_{10}	0.497 (38.8)		
VP1 (L)	Θ_4	2.54 (8.2)	34.64 (47.0)	NE
Weight	...	1 FIX		
Q3 (1/h)	Θ_5	6.27 (4.0)	49.30 (23.8)	NE
Weight	...	0.75 FIX		
VP2 (L)	Θ_6	113 (3.7)	41.71 (19.8)	12.24 (47.7)
Weight	...	1 FIX		
CCV Residual Error (as %CV)		20.4 (6.0)		

* - SE given as %CV; NE - Not Estimated

(Source: Sponsor's Population PK Report, Apendix III, Table 14, Pg 122)
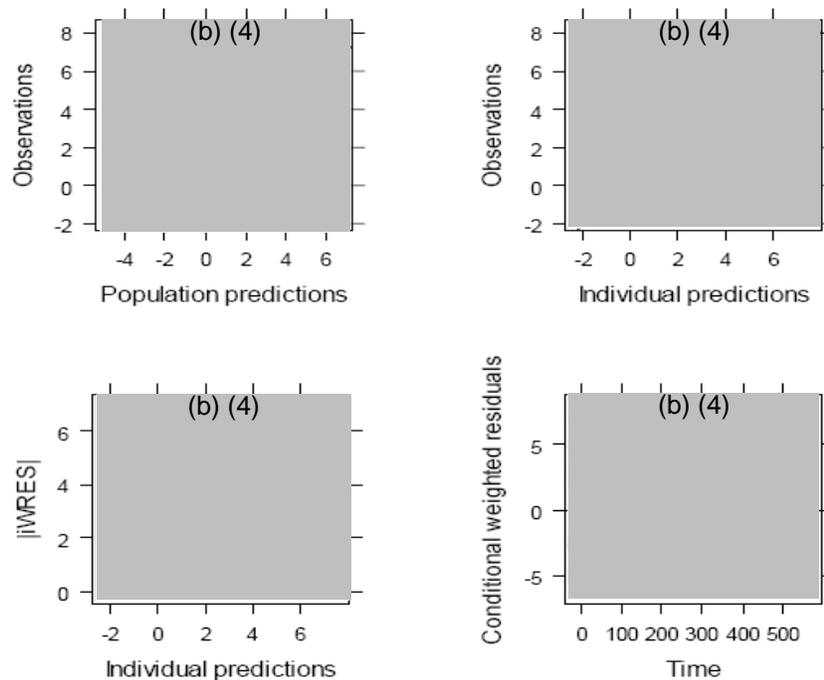
Figure 13: Basic goodness of fit plots for the Sponsor's final model.

(Source: Sponsor's Population PK Report, Apendix III, Figure 18, Pg 141)

4.2   GENOMICS REVIEW

GENOMICS REVIEW

NDA Number	201-532
Submission Type	Priority
Applicant Name	Eisai Inc.
Submission Date	March 30, 2010
Generic Name	Eribulin mesylate
Proposed Indication	Locally advanced or metastatic breast cancer who have previously received at least two chemotherapy regimens, including an anthracycline and a taxane for locally advanced or metastatic breast cancer
Primary Reviewer	Stacy Shord, Pharm.D.
Secondary Reviewer	Issam Zineh, Pharm.D., M.P.H.

Table of Contents

1 BACKGROUND

Eribulin (eribulin mesylate or E7389) is a new molecular entity that inhibits microtubule growth leading to nonproductive tubulin aggregates (see header for indication). The dose-limiting toxicities observed were neutropenia, febrile neutropenia and fatigue. Eribulin exposure is related to neutropenia and peripheral neuropathy based on our population pharmacokinetic-adverse event (PK/AE) analysis.

Excretion: Eribulin's major elimination pathway in humans is fecal (82% of the dose; 88% as eribulin). Renal elimination and metabolism represent minor contributions; biliary excretion is purported to substantially contribute to eribulin clearance based on non-clinical ADME studies in which 36% of the administered radiolabeled dose was recovered in the bile within 72 hours. Eribulin undergoes negligible metabolism based on the human ADME study (E7389-E044-103), but cytochrome P450 (CYP) 3A4 is responsible for the limited metabolism of eribulin based on studies conducted in human liver microsomes. A drug-drug interaction study (E7389-E044-109) demonstrated that eribulin's area under the concentration vs. time curve ($AUC_{0-\infty}$) was similar when administered in combination with ketoconazole, a strong CYP3A4 inhibitor. The applicant's population PK/pharmacodynamic (PD) analysis indicates that eribulin clearance appears similar between patients taking CYP3A4 inducers and inhibitors compared to patients not taking concomitant medications affecting CYP3A4 metabolism.

Coefficient of Variation: The systemic clearance of eribulin demonstrated inter-patient variability of 54%. The population PK analysis demonstrates that eribulin clearance is affected by body weight and serum albumin, alkaline phosphatase and bilirubin concentrations; but these variables only reduced the interpatient variability in clearance from 54% to 45%. This inter-patient variability is not likely explained by variability in metabolic capacity, since eribulin undergoes limited hepatic metabolism. Furthermore, the following enzymes are not responsible for the limited metabolism of eribulin based on *in vitro* studies: CYP19, CYP1A1, CYP1A2, CYPB1, CYP2A6, CYP2B6, CYP2C18, CYP2C19, CYP2C8, CYP2C9, CYP2E1, CYP3A5, CYP4A11, CYP4F2, CYP4F3B, FMO1, FMO3, FMO5, UGT1A1, UGT1A3, UGT2B7, GSTA1-1, NAT1, NAT2, and SULT1A1.

Drug Transport: Eribulin is a substrate and a weak inhibitor of the drug transport protein P-glycoprotein (Pgp). The cell growth of drug sensitive and drug resistant human uterine cancer cells were grown in the presence and absence of eribulin for 96 hours and cell growth was assessed (study no. CAIVT0105 and CAIVT0106). Drug resistant cells were 2670-fold less sensitive to eribulin than drug sensitive cells. Verapamil, a Pgp inhibitor, was able to markedly increase the sensitivity of the drug resistant cells to eribulin. Drug resistant cells were 427-fold less sensitive to eribulin than the drug sensitive cells in the presence of verapamil. The ratio of the C_{max} reported for the proposed clinical dose to the mean IC_{50} value indicates that eribulin will likely be transported by Pgp in humans.

2 NDA CONTENT RELATED TO GENOMICS

The applicant conducted three dose escalation trials and seven additional clinical trials to support the clinical pharmacology evaluation. Genomic data on metabolic status were included in three of these clinical trials (study 103, 108 and 109) and genomic data on tumoral expression of β-tubulin isotypes and other related proteins were included in two of these clinical studies (study NCI-5730 and 201). The clinical trials that incorporated genomic data are listed in appendix 1.

3   KEY QUESTIONS AND SUMMARY OF GENOMICS FINDINGS

3.1   ARE TUMOR GENOMIC BIOMARKERS ASSOCIATED WITH CLINCIAL OUTCOMES?

Not definitively. While there was an inverse relationship between β-tubulin 3 (BTcIII) and best response in patients diagnosed with metastatic breast cancer, it is unclear whether these markers are prognostic or predictive of eribulin response.

3.1.1   Tumoral Expression Microtubule Proteins

Microtubules are cytoskeleton structures integral to cell division. The basic structural units are tubulin heterodimers made up from α- and β-tubulin. Several tubulin subtypes (isotypes) have been identified. Post-translational modifications of these subtypes can alter the interaction of microtubules with microtubule-associated proteins (MAP) and change their function. Stathmin is a highly conserved 17 kDa protein that regulates rapid microtubule remodeling of the cytoskeleton and MAP4 is a protein that promotes microtubule assembly and has been shown to counteract destabilization of interphase microtubule catastrophe promotion.

β-tubulin expression is disrupted in cancer cells and overexpression or aberrant expression of BTcIII can affect the response of tumor cells to tubulin binding agents, such as vinca alkaloids and taxanes. Proteins that regulate microtubules, such as MAPs and stathmin, are also implicated in drug resistance. The mechanisms that mediate this resistance are currently being explored. [Kavallaris. Nat Rev Cancer 2010]

Tumoral expressions of the molecular targets of eribulin were assessed in two clinical trials: NCI-5730 and study 201.

3.1.2   NCI-5730

Forty patients diagnosed with advanced, histologically-confirmed solid tumors were enrolled into this dose escalation clinical trial. Thirty-four patients were White, five were Asian, and one was Black. Following determination of the MTD, an additional 13 patients were accrued to obtain pre- and post-treatment biopsy material to validate the molecular targets of eribulin.

Blood and fresh tumor biopsies were obtained before the first cycle. A repeat tumor biopsy, whenever feasible, was obtained between one and twenty-four hours following the first dose. Serial pre- and post-treatment formalin fixed paraffin-embedded tissue specimens were sent to (b) (4) for quantitative PCR analysis of β-tubulin isotypes (III, IVb, V, and VI), MAP4, and stathmin expression.

Thirty-six serial biopsies specimens were obtained from 13 patients enrolled in an expanded cohort treated at the MTD. The applicant stated that because gene expression from specimens collected pre-treatment and post-treatment did not vary significantly and because pre-treatment specimens were not available from all patients, the data was reported as the average gene expression for all samples collected from each patient. The applicant concluded that there is preliminary evidence to suggest that lower intra-tumoral levels of BTcIII or higher intra-tumoral levels of MAP4 may correlate with response to eribulin, while lower intra-tumoral levels of stathmin may be associated with progression (**Figure 1**).

Figure 1. Tumoral expression of β-tubulin III (panel A), MAP4 (panel B) and stathmin (panel C) versus best response
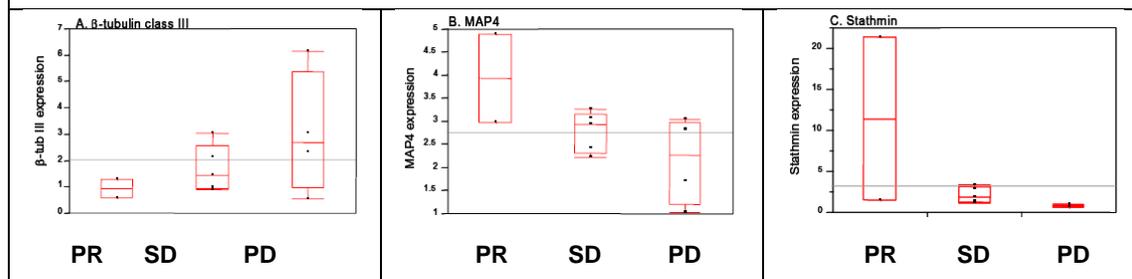
Source: NCI-5730 manuscript, figure 6, page 41

PR = partial response; SD = stable disease; PD = progressive disease

A clinical study report and data files were not provided. The information regarding this clinical trial was provided as an unpublished manuscript. The appropriateness of the applicant's decision to average the gene expression for all samples collected is unknown, since the coefficient of variation of the expression of the tumoral proteins and the effect of eribulin on these proteins has not been previously ascertained. Given there was no comparator arm in this study, there is insufficient evidence that intratumoral levels are predictive of drug response solely based on these data.

3.1.3   Study 201

One hundred four women with metastatic breast cancer previously treated with an anthracycline and a taxane were enrolled into this open-label, single-arm, multi-center clinical trial (87 analyzed for efficacy; 103 analyzed for safety). Seventy-two patients were White, 12 were Hispanic, 11 were Black, five were Asian/Pacific and three were other. Additional consent was required to allow pharmacogenetic analysis of available diagnostic biopsy samples. Tumor assessments were performed according to the Response Criteria in Solid Tumors (RECIST) at baseline, every two cycles and whenever there was clinical evidence of disease progression. The relative expression levels of various β-tubulin isotypes, stathmin and MAP4 in the tumors of the patients were correlated with sensitivity to eribulin on the basis of patients' responses to treatment.

The expression levels of three β-tubulin isotypes (BTcIII, IVb, and V), MAP4, and stathmin were assessed in tumor tissue collected from 34 patients. Of these 34 patients, 26 patients had data for all of the variables. The biopsy material was obtained from the primary tumor surgery completed for the diagnosis or treatment of the cancer. The applicant determined the individual and joint effects of the relative gene expression on overall survival (OS) and progression (PFS) free survival using Cox's proportional hazards regression model and simple linear logistic regression.

For the analysis of OS, when all five covariates are added in the model, the applicant found that the most significant covariate was BTcIII, followed by stathmin, BTcIVb, MAP4, BTcV. When the five covariates were analyzed separately, the most significant covariate was BTcIII, followed by stathmin, and then followed by BTcV, BTcIVb, and MAP4. Out of the five covariates, BTcIII was the only covariate that achieved statistical significance of <0.05 when assessed individually. When assessed jointly, the significance of BTcIII was reduced to marginally significant (P =

0.050). For the analysis of PFS, when all five covariates are added in the model, two covariates showed statistical significance: BTcV had P-value of 0.002, and MAP4 had P-value of 0.041. When assessed individually, none of the covariates showed statistical significance.

For the analysis of tumor response, the applicant found that none of the covariates achieved statistical significance. Our analysis demonstrates a possible inverse relationship between BTcIII and BTcIV basal expression and best response (**Figure 2**). No apparent relationship was observed between MAP4 or stathmin expression and best response in this small study population.

The applicant concluded that these data provide some supporting evidence for possible associations of the pair BTcIII and stathmin with OS, of the pair MAP4 and BTcIII with PFS, and of BTcIVb with tumor response. Of these gene expression levels, only the association of BTcIII with OS showed potential statistical significance; BTcIII was negatively associated with OS.

**Figure 2.** Tumoral expression of β-tubulin III (top left), β-tubulin IVb (top right), MAP4 (bottom left) and stathmin (bottom right) versus overall and progression-free survival
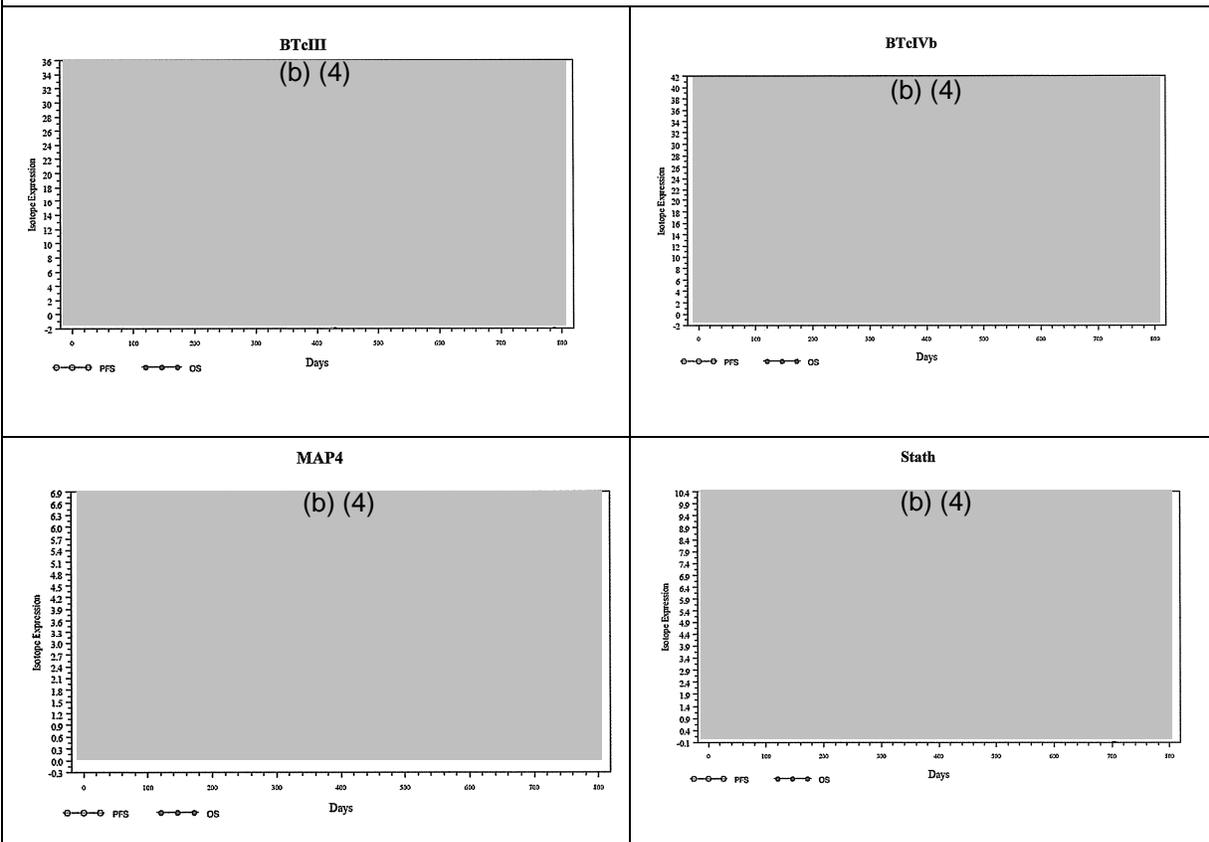
Source: E7389-A001-201 pharmacogenomics report, figure 1, pages 10, 12

Figure 3. Tumoral expression of β-tubulin III (top left), β-tubulin IV (top right), MAP4 (bottom left) and stathmin (bottom right) versus best response
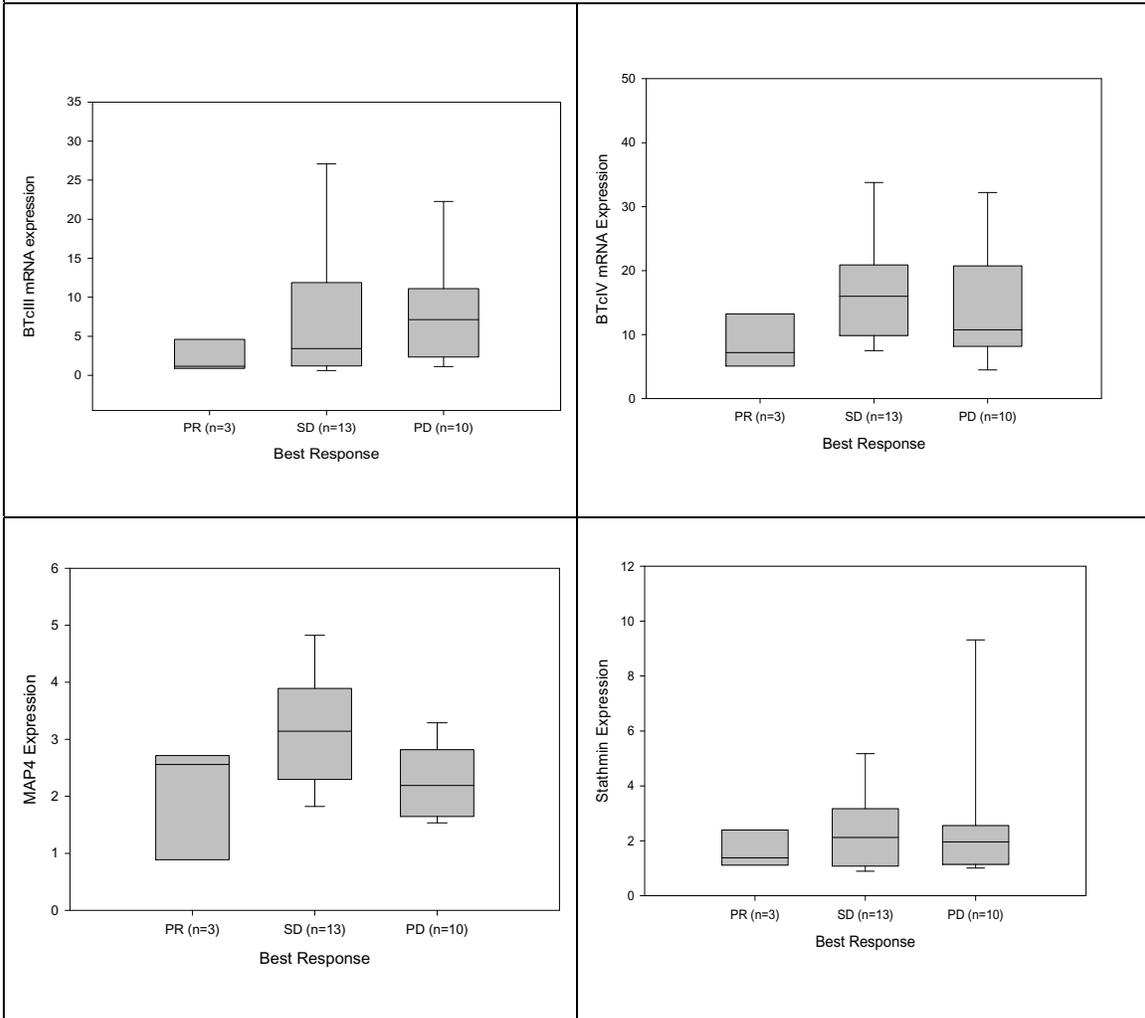
PR = partial response; SD = stable disease; PD = progressive disease

Source: our analysis

3.1.4   Summary and Conclusions

Tumor biomarkers were collected in two clinical trials and data was available from 47 patients. The data suggest a potential inverse relationship between the basal expression of BTcIII and best response in patients diagnosed with metastatic breast cancer. However, these findings need to be interpreted with caution due to the lack of comparator arm in this trial. The predictive value of these markers is not known, since pre- and post-treatment tumor biopsy materials were not routinely collected from the patients enrolled into these trials. Additional comments will be conveyed to the applicant to suggest that the predictive and prognostic relationship of these tubulin biomarkers be examined in ongoing and future clinical trials.

Additionally, we will include a comment for the applicant to consider examining the prognostic and predictive value of P-glycoprotein (P-gp) expression in the tumor in the same clinical trials. Nonclinical studies conducted by the applicant demonstrate that P-gp overexpression is associated with resistance to eribulin; furthermore, these cells were resistant to taxanes and vincas suggesting a possible cross-resistance.

3.2 WAS THE PHARMACOGENOMIC ASSESSMENT OF ADME GENES ADEQUATELY CONDUCTED?

No. The rationale for studying CYP3A and CYP2C9 genetic variants is unclear given the negligible role of hepatic metabolism in eribulin clearance. Nonetheless, variants in CYP3A and CYP2C9 did not appear to contribute to variable eribulin PK in this limited sample set.

CYP3A4 and CYP3A5 genotype were identified in three trials and CYP2C9 genotype was identified in one trial.

3.2.1 Study 103

Six patients with advanced solid tumors who had progressed following standard therapy or for which no standard therapy existed were enrolled into an open-label, non-randomized, single-center clinical trial to determine the metabolism and elimination of ^{14}C-eribulin. All patients enrolled were White. Blood samples taken at the screening visit were retained for pharmacogenomic analysis and enzyme polymorphism testing. The relationship between CYP3A (both CYP3A4 and CYP3A5) and CYP2C9 predicted phenotypes and eribulin exposure was investigated, but no formal statistical analysis was planned.

The presence of the following variants were identified: *CYP3A4*1B, CYP3A4*7; and CYP3A5 *1B, *1C, *2, *3, *3B, *6; and CYP2C9*2, *3, *5, *6.* These variant alleles appear to be appropriately selected, since the more common alleles found in Whites are included for identification.

The majority of patients (5/6) were carriers of the *CYP2C9 *1/*1* and *CYP3A4 *1/*1* genotypes, and were classified by the applicant as CYP2C9 and CYP3A4 extensive metabolizers. One patient was identified as a carrier of *CYP3A4*1B* and a carrier of *CYP2C9*2.* The allele frequency of *CYP3A4*1B* in Whites is ~11% [Lamba, et al Pharmacogenetics 2002] and the allele frequency of *CYP2C9*2* in Whites is ~8% to 13% [Mizutani. Drug Metab Rev 2003]; the frequency in this study population is about 8% for each of these alleles and consistent with published reports.

Most patients (5/6) were *CYP3A5* non-expressors; one patient was identified as a carrier of *CYP3A5*1.* The allele frequency in this study population appears consistent with the published literature [Kuehl, et al. Nat Genet 2001]. *CYP3A5* expression does not appear to effect eribulin clearance; the clearance of eribulin in this patient (2.16 L/hr/m^2) was only 10% higher than the median clearance of the remaining five non-expressers (1.96 L/hr/m^2).

3.2.2 Study 108

Eighteen patients diagnosed with advanced solid tumors who had progressed following standard therapy or for whom no standard therapy existed and who had normal or reduced hepatic function according to the Child-Pugh system were enrolled into this open-label, parallel group clinical trial to explore the pharmacokinetics of eribulin mesylate. All patients enrolled were White. Patients were assigned to one of three groups: normal hepatic function, mild hepatic

impairment (Child-Pugh A) and moderate hepatic impairment (Child-Pugh B) according to the Child-Pugh System for classifying hepatic impairment.

A blood sample was taken before dosing on day 1 of cycle 1 to identify *CYP3A4* and *CYP3A5* genotype for each individual using a haplotyping approach. The applicant classified each patient as an extensive, intermediate or poor metabolizer based on their genotype. For *CYP3A4*, carriers of a *1/*1* genotype were classified as extensive metabolizers and *1/N* genotype were classified as intermediate metabolizers. For *CYP3A5*, carriers of the *3/*3* genotype were classified as poor metabolizers and carriers of *3/N* were classified as intermediate metabolizers. The variant alleles identified were *CYP3A4*1B* and *7 and *CYP3A5*1B, *1C, *2, *3, *3B* and *6*. An exploratory analysis of patient's *CYP3A* genotype with exposure to eribulin was planned by the applicant.

Figure 4. Effect of CYP3A4 and CYP3A5 metabolizer status on eribulin exposure
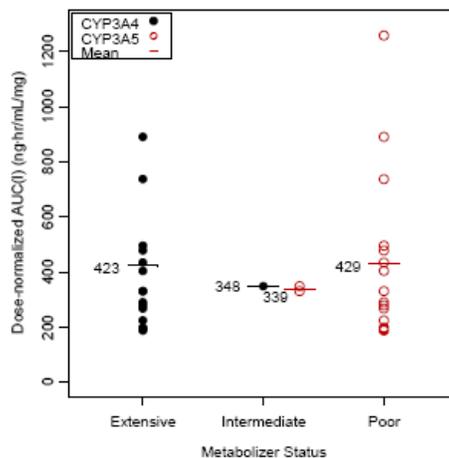
Source: revised Clinical study report E7389-E044-108, figure 4, page 14

Seventeen patients were carriers of the *CYP3A4 *1/*1* genotype and were classified by the applicant as extensive metabolizers; the frequency of the *1* allele is consistent with published reports (~95%). Sixteen patients were identified as *CYP3A5* non-expressers. The frequency of the *CYP3A5*1* variant allele is ~6% in this population and is consistent with published reports (~5%) [Roy et al. Drug Metab Dispos 2005]. One patient was heterozygous for *CYP3A5*3* allele (*3/*1). The remaining patient was heterozygous for *CYP3A4 *1* (*1/*1B) and heterozygous for *CYP3A5*3* allele (*3/*1). The patient should be identified as a *CYP3A5* expressor.

The dose-normalized AUC appears similar between the patients identified as a *CYP3A5* expressors compared to the remaining patients identified as non-expressers. Clearance could not be compared between the expressor and non-expressers, since hepatic impairment is associated with reduced clearance of the parent compound and the individual patient identified as a non-expressor has moderate hepatic impairment.

3.2.3   Study 109

Twelve patients with histologically or cytologically confirmed advanced solid tumors who had progressed following standard therapy or for which no standard therapy existed were enrolled into this randomized, open-label, 2-treatment, 2-sequence, 2-way crossover clinical trial. All patients enrolled were White.

A blood sample was taken prior to dosing on day 1 of cycle 1 to assess the *CYP3A4* and *CYP3A5* genotype for each individual using a haplotyping approach. The variant alleles identified were *CYP3A4*1B* and *7* and *CYP3A5*1B, *1C, *2, *3, *3B* and *6*. The relationship between CYP3A predicted phenotypes and eribulin exposure was investigated, but no formal statistical analysis was planned.

All 10 patients assessed for genotyping were classified as extensive metabolizers for CYP3A4 and poor-metabolizers of CYP3A5 by the applicant. The allele frequency for *CYP3A4*1* and *CYP3A5*3* appear consistent with the published literature for white populations. No association between genotype and pharmacokinetic data was conducted, due to the absence of sequence variability in this study population.

Figure 5. Effect of CYP3A4 and CYP3A5 metabolizer status on eribulin exposure
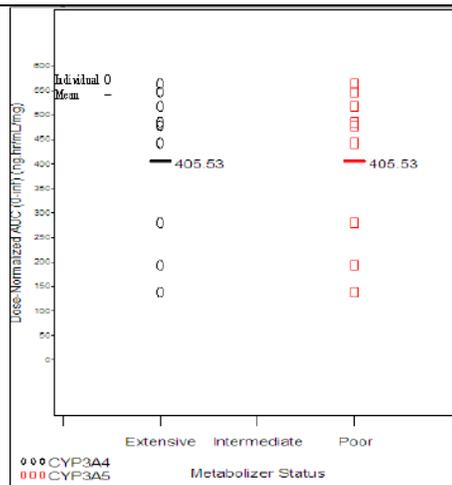
Source: Clinical study report E7389-E044-109, figure 14.2.5, page 1

3.2.4 Summary and Conclusions

It is not clear why the applicant selected CYP2C9 for pharmacogenomic analysis, since eribulin does not undergo metabolism by this enzyme. It is also not clear why the applicant selected to identify variants of CYP3A4 and CYP3A5, since eribulin undergoes negligible metabolism. Furthermore, the effects of CYP3A4 variant alleles on drug metabolism is not well understood and few White individuals express CYP3A5 (95% non-expressers).

The coefficient of variation is relatively high at 54%. The applicant identified a few variables associated with eribulin clearance, but these variables only explain about 9% of the variability. An additional comment that will be conveyed to the applicant suggests that the applicant collect germline DNA for pharmacogenetics analysis of potential drug targets and transporters be collected in ongoing and future clinical trials.

4 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the current NDA submission for eribulin mesylate for the proposed indication of locally advanced or metastatic breast cancer. No post-marketing requirements or commitments are recommended at this time.

The FDA recommends the following **additional comments be conveyed to the applicant**:

- Characterize the predictive and/or prognostic relationship between β-tubulin, microtubule associated proteins, and P-gp mRNA expression in tumors within ongoing and future randomized, controlled trials.

- Collect germline DNA to enable future pharmacogenetic analyses of eribulin response and tolerability (e.g. neuropathy) in ongoing and future clinical trials.

5   LABEL RECOMMENDATIONS

Only relevant genomics sections are included. ~~Srikethroughs~~ indicate content taken out from the proposed label.

12   CLINICAL PHARMACOLOGY

   12.1   Mechanism of Action

(b) (4)

Signatures:

Stacy S Shord, Pharm.D.   Issam Zineh, Pharm.D., M.P.H.

Reviewer, Genomics Group   Associate Director, Genomics Group
Office of Clinical Pharmacology 5   Office of Clinical Pharmacology 5

Cc: DCP-5:   CTL - H Zhao**; DDD -** B Booth**; DD -** A Rahman

APPENDIX 1

Table 1. Summary of clinical trials with content related to genomics					
Study Number	**Primary Study Objective**	**Study Design**	**Patient Number**	**Treatment**	**Genomic Data**
Tumor Biomarkers					
NCI-5730	To determine the MTD, describe the toxicities of E7389, evaluate the PK of E7389, determine the anti-mitotic activity of E7389 and document clinical responses to E7389	Open-label, non-randomized, dose titration study	40	0.125 to 2 mg/m^2 as an IV bolus over 1-2 minutes weekly for 3 weeks, repeated every 4 weeks	β-tubulin MAP4 stathmin
Study 201	To determine the efficacy, quality of life, pharmacogenetics, safety and tolerability of E7389 in patients with advanced/ metastatic breast cancer	Open-label, single-arm, multi-center study	104	1.4mg/m^2 as a 5 minute IV bolus on weekly, for 3 weeks, every 4 weeks or for 2 weeks, every 3 weeks	β-tubulin III MAP4 stathmin
Cytochrome P450 Enzymes					
Study 103	To determine the excretion balance and elucidate the metabolic pathway of eribulin after a single dose of ^{14}C-E7389 in patients with advanced solid tumors	Open-label, single center, single arm Human ADME Study	6	^{14}C-E7389 acetate 2 mg as an intravenous infusion on Day 1.	CYP2C CYP3A4 CYP3A5
Study 108	To study the effects of hepatic impairment on plasma PK parameters of E7389 and to explore safety and tolerability in patients with reduced hepatic function	Open-label, multi-center, single arm Hepatic Impairment Study	16	Normal hepatic function: 1.4mg/m^2 Mild impairment: 1.1mg/m^2 Moderate impairment: 0.7mg/m^2 as an IV bolus over 2-5 minutes on Days 1 and 8 of a 21-day cycle	CYP3A4 CYP3A5
Study 109	To study the influence of repeated oral administration of ketoconazole, a potent CYP3A4 inhibitor, at a therapeutic dose on the plasma PK of eribulin administered by IV infusion.	Open-label, non-randomized, single-center study	12	E7389 Group 1: 1.4 mg/m^2 on Day 1 and 0.7 mg/m^2 on Day 15 Group 2: 0.7 mg/m^2 on	CYP3A4 CYP3A5

				Day 1 and 1.4 mg/m^2 on Day 15.	
				Ketoconazole	
				Group 1: 200 mg on Days 15 and 16	
				Group 2: 200 mg on Days 1 and 2	

4.3 SAFETY REVIEW

NDA 201532

From: OCP Safety Review Team

To: OCP Division 5

Subject: Safety Review of NDA 201532 (Eribulin Mesylate for injection)

Safety Group's Comments We recommend that the sponsor investigate whether genes of glutathione S-transferases are associated with eribulin-induced neurotoxicity, especially the *GSTP* gene. Other genes involved in the cellular oxidative-stress pathway may also be worthy of investigation.

Most frequently reported treatment-related adverse events neutropenia (55%), asthenia+fatigue (53%), alopecia (50%), nausea (35%), and peripheral neuropathy (35%). The incidence frequency of Grade 3+4 febrile neutropenia was 5%, peripheral neuropathy 7%, and asthenia+fatigue 8%.

Genes involved in chemotherapy-induced neurotoxicity The *GSTP1* 105Ile/105Ile genotype was reportedly associated with the development of grade≥ 2 docetaxel-induced peripheral neuropathy (odds ratio of 6.5) (Mir et al., 2009). Other reports also identified homozygous *GSTP1* I105V genotype as a risk factor for neurotoxicity related to FU plus oxaliplatin or irinotecan plus oxaliplatin treatment, and for oxaliplatin-related cumulative neuropathy (McLeod et al., 2010; Lecomte et al., 2006). *GSTM1* and *GSTT1* polymorphisms have been suggested to predict adverse events (including neurotoxicity) in children who received treatment with cisplatin, cyclophosphamide, and vincristine (Barahmani et al., 2008).

The involvement of genes associated with the oxidative-stress pathway is supported by another report. The oxidative-stress pathway reportedly was involved in the efficacy and toxicity of cyclophosphamide-containing adjuvant chemotherapy and manganese superoxide dismutase (encoded by gene *SOD2*), and the Val16Ala allele of *SOD2* was reportedly related to less treatment-related toxicity, neutropenia (Yao et al., 2010).

Mechanism for Neuropathy: Neural cells do not divide. Eribulin (E7389) shared similar mechanism of actions with paclitaxel and vinblastine, and they all bind to tubulin and disrupt microtubule dynamics. Microtubules are key components of many cellular processes including axonal transport. For vinca alkaloids and taxane, damage to dorsal root ganglion, microtubule-associated toxicity, mitochondrial dysfunction, and distal axonal injury have been suggested (Part et al., 2008). Vinblastine reportedly caused microtubule destabilization, tubulin degration mediated by proteasome in neural cells (Huff et al 2010). Behaving like vinca alkloid, eribulin inhibited GTP binding to tubulin and tubulin-dependent GTP-hydrolysis (Dabydeen et al., 2006).

Eribulin, like paclitaxel, caused phosphorylation and inactivation of Bcl-2 (antiapoptotic protein), cytochrome c relase from mitochondria, activation of caspase-3 and -9, leading to mitochondrial apoptotic pathway (Kuznetsov et al 2004). Paclitaxel reportedly caused mitochondrial dysfunction, therefore contributing to neuropathy (Flatters et al., 2006).

Association of oxidative-stress pathway genes with drug-induced toxicity:
Glutathione S-transferases (GSTs) were suggested to detoxify free oxygen radicals induced by chemotherapy (Hayes et al., 1995). Reportedly, resistance to docetaxel in breast cancer could be mediated by the activation of several genes involved in cellular redox environment (Iwao-

Koizumi et al., 2005). Paclitaxel reportedly induced production of reactive oxygen species by activating NADPH oxidase which is regulated by Rac GTPase, a member of Roc GTPase family closely interacting with microtubule (Alexandre at al 2006). Glutathione synthesis inhibitor significantly increased paclitaxel cytotoxicity and H2O2 accumulation. Furthermore, paclitaxel interacted with mitochondrial tubulin and disrupted the mitochondrial respiratory chain. In all, paclitaxel activated NADPH oxidase and induced production of superoxide anions and H2O2, leading to cell apoptosis. Production of reactive oxygen species involving NADPH oxidase is shown below.


from www.nature.com

Coupling of GSH redox cycle to NADPH supply is shown below. During peroxide elimination, the regeneration of GSH from GSSG is maintained by the GSH peroxidase and GSSG reductase system, the GSH redox cycle

Oxidative-Stress pathway

Fig. 1 Reactive oxidative species (ROS) metabolism pathway. *Variant*: nonsynonymous coding SNP rs4880 of *SOD2* gene, T (Valine) → C (Alanine). *Function*: C variant associated with better mitochondrial targeting. *Hypothesis*: C variant associated with less toxicity but poorer survival after treatment

CAT: catalase, GPX: glutathione peroxidase, MPO: myeloperoxidase, HOCl: hypochlorous acid (Yao et al., 2010).

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JANE PF BAI
08/09/2010

DARRELL ABERNETHY
08/09/2010

4.4   PRODUCT LABEL

4.5   STUDY REPORTS

4.6   CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM FOR NDA

These appendices are contained in a separate document.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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/s/

STACY S SHORD
08/19/2010

HONG ZHAO
08/19/2010
I concur.

Anshu Marathe
08/19/2010

CHRISTINE E GARNETT
08/19/2010

ISSAM ZINEH
08/19/2010

NAM ATIQUR RAHMAN
08/24/2010