Report on the Deliberation Results

February 1, 2011
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Halaven Injection 1 mg
[Non-proprietary name]	Eribulin Mesilate (JAN*)
[Applicant]	Eisai Co., Ltd.
[Date of application]	March 30, 2010

[Results of deliberation]
In the meeting held on January 20, 2011, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological or specified biological product. The re-examination period is 8 years. The drug substance and drug product are both classified as poisonous drugs.

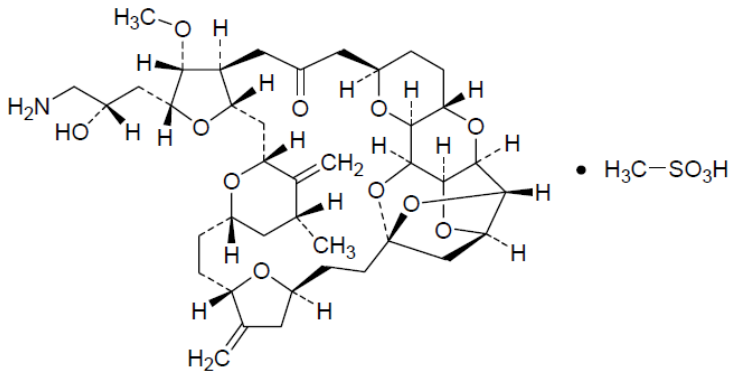
**Japanese Accepted Name (modified INN)*

Review Report

January 12, 2011
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows:

[Brand name]	Halaven Injection 1 mg
[Non-proprietary name]	Eribulin Mesilate
[Applicant]	Eisai Co., Ltd.
[Date of application]	March 30, 2010
[Dosage form/Strength]	Injectable solution: each vial contains 1.0 mg of eribulin mesilate
[Application classification]	Prescription drug, (1) Drug with a new active ingredient
[Chemical structure]	



Molecular formula: $C_{40}H_{59}NO_{11}\cdot CH_4O_3S$

Molecular weight: 826.00

Chemical name:

(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*)-2-[(2*S*)-3-Amino-2-hydroxypropyl]-3-methoxy-26-methyl-20,27-dimethylidenehexacosahydro-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 monomethanesulfonate

[Items warranting special mention]

Priority review (PFSB/ELD Notification No. 0518-13 dated May 18, 2010, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour, and Welfare)

[Reviewing office] Office of New Drug V

Review Results

January 12, 2011

[Brand name] Halaven Injection 1 mg
[Non-proprietary name] Eribulin Mesilate
[Applicant] Eisai Co., Ltd.
[Date of application] March 30, 2010
[Results of review]
The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the submitted data demonstrate the efficacy of the proposed product in treating inoperable or recurrent breast cancer and its acceptable safety in view of its observed benefits. Safety concerns including bone marrow depression, serious infections, peripheral nerve disorders, hepatic function disorder, and interstitial lung disease should be further investigated through post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication, and dosage and administration shown below:

[Indication]
Inoperable or recurrent breast cancer

[Dosage and administration]
The usual adult dosage is 1.4 mg/m^2 (body surface area) of eribulin mesilate administered intravenously over 2 to 5 minutes once weekly for 2 consecutive weeks, followed by a rest week. This treatment cycle is repeated. The dose may be adjusted according to the patient's condition.

Review Report (1)

November 17, 2010

I. Product Submitted for Registration

[Brand name]	Halaven Injection 1 mg
[Non-proprietary name]	Eribulin Mesilate
[Applicant]	Eisai Co., Ltd.
[Date of application]	March 30, 2010
[Dosage form/Strength]	Injectable solution: each vial contains 1.0 mg of eribulin mesilate
[Proposed indication]	Inoperable or recurrent breast cancer

[Proposed dosage and administration]

The usual adult dosage is 1.4 mg/m^2 (body surface area) of eribulin mesilate administered intravenously over 2 to 5 minutes once weekly for 2 consecutive weeks, followed by a rest week. This treatment cycle is repeated. The dose may be adjusted according to the patient's condition.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

1.(1) Summary of eribulin mesilate

Eribulin mesilate is a derivative (fully synthetic active portion) of halichondrin B (HalB) that was isolated from a marine sponge *Halichondria okadai* Kadota and structurally characterized by Hirata and Uemura in 1985. (The marine sponge was collected in Aburatsubo, Miura Peninsula, Kanagawa Prefecture in Japan.) Eribulin mesilate is considered to inhibit tubulin polymerization and suppress microtubule growth to disrupt the function of the spindle apparatus. This causes cell cycle arrest in the second gap/mitosis phase (G2/M phase) to induce apoptosis, thereby inhibiting tumor growth.

1.(2) History of development

In the US, the National Cancer Institute (NCI) started a phase I study in patients with solid tumors (Foreign Study NCI-5730) in August 2002. Eisai Medical Research Inc. (currently Eisai Inc.) in the US started phase I studies (Foreign Studies E7389-A001-101 and E7389-A001-102) in August 2003. In the breast cancer field, 2 phase II studies in patients with advanced or recurrent breast cancer (Foreign Studies E7389-A001-201 and E7389-G000-211) were started in November 2004. Based on the results

of these 2 studies, 2 phase III studies in patients with advanced or recurrent breast cancer (Foreign Studies E7389-G000-[redacted] and E7389-G000-305) were started in September 2006.

In Japan, a phase I study in patients with solid tumors (Japanese Study E7389-J081-105) was started in May 2006 when the foreign phase II studies were underway. A phase II study in patients with advanced or recurrent breast cancer (Japanese Study E7389-J081-221) was started in January 2008.

Recently, based mainly on the results of Foreign Study E7389-G000-305, a marketing application for eribulin mesilate has now been filed around the same time in Japan, the US, and Europe. As of October 2010, eribulin mesilate has not been approved in any country or region. Foreign Study E7389-G000-[redacted] is currently underway (enrollment was completed in [redacted] 20[redacted]. The second interim analysis was conducted in [redacted] 20[redacted] and the final analysis in 20[redacted]. The study results are expected to be finalized in [redacted] 20[redacted]). No data from the study were submitted for this application.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

(a) General properties

The following general properties of the drug substance have been determined: description, solubility, distribution coefficient, acid dissociation constant (pKa), optical rotation, melting point, hygroscopicity, stability in an aqueous solution, and crystallinity.

Eribulin mesilate is a white powder. It is freely soluble in water and ethanol (99.5), soluble in acetone, sparingly soluble in acetonitrile, and practically insoluble in *n*-heptane. It is freely soluble in pH 3 to 7 buffer, soluble in pH 9 buffer, and slightly soluble in pH 11 buffer. Its distribution coefficient is 2.25 (1-octanol/buffer; ionic strength, 0.3); pKa is 9.55; optical rotation is −179°; and its melting point is approximately 160°C (degradation). It is hygroscopic and degraded by acid and heat. The residual rate of eribulin mesilate in a 0.5-mg/mL eribulin mesilate solution (buffer, 5% ethanol; ionic strength, 0.3; pH 3) after storage at [redacted]°C for [redacted] weeks was [redacted]%. Eribulin mesilate is amorphous.

(b) Structural determination

The chemical structure of eribulin mesilate were elucidated by ion chromatography, ultraviolet spectroscopy, infrared spectrophotometry (IR), mass spectrometry (MS), nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR), single-crystal X-ray diffraction analysis, and circular dichroism spectroscopy.

2.A.(1).2) Manufacturing process

(a) Manufacturing steps

Eribulin mesilate is manufactured in the following [redacted] steps from Starting Materials 1[*1] and 2[*2] at the Kashima Plant of Eisai Co., Ltd.:

[redacted]

Step [redacted]: Synthesis of [redacted]

[redacted] is added to Starting Material 1, [redacted], to allow reaction. Acetone and methanol are added to stop the reaction. The organic layer is separated, washed, and concentrated and then purified by silica gel column chromatography to obtain [redacted].

Step [redacted]: Synthesis of [redacted]

[redacted] is added to a tetrahydrofuran (THF) solution of Starting Material 2, then [redacted] is added to allow reaction. Ammonium chloride solution is added to stop the reaction. The organic layer is separated, washed, and concentrated and then dissolved in *n*-heptane. The *n*-heptane layer is washed with acetonitrile (ACN) to obtain [redacted].

Step [redacted]: Synthesis of [redacted]

[redacted] is added to [redacted] to allow reaction. Sodium hydrogen carbonate solution and sodium sulfite solution are added to stop the reaction. The organic layer is separated, concentrated, and then purified by silica gel column chromatography to obtain [redacted].

Step [redacted]: Synthesis of [redacted]

[redacted] is added to [redacted] to allow reaction. Mixed solution of potassium carbonate and potassium sodium tartrate is added to stop the reaction. The organic layer is separated, washed, and concentrated and then purified by silica gel column chromatography to obtain [redacted].

Step [redacted]: Synthesis of [redacted]

[redacted] is added to [redacted]. [redacted] and [redacted] are sequentially added to this solution to allow reaction. After the addition of *n*-heptane, the reaction mixture is filtrated and washed

with *n*-heptane and ACN. The filtrate is then separated and the ACN layer is extracted with *n*-heptane. The layers of the mixed *n*-heptane are washed with ACN and concentrated to obtain [redacted].

Step [redacted]: Synthesis of [redacted]

[redacted] is added to [redacted] to allow reaction. Sodium hydrogen carbonate solution and sodium sulfite solution are added to stop the reaction. The organic layer is separated, concentrated, and then purified by silica gel column chromatography to obtain [redacted].

Step [redacted]: Synthesis of [redacted]

[redacted] is added to [redacted] to allow reaction. Toluene and water are added to stop the reaction. The organic layer is then separated and concentrated to obtain [redacted].

Step [redacted]: Synthesis of [redacted]

[redacted] is added to a DCM solution of [redacted] to allow reaction. The reaction mixture is purified by silica gel column chromatography to obtain [redacted], which is further purified by crystallization from an ACN/water mixture.

Step [redacted]: Synthesis of [redacted]

[redacted], [redacted], and [redacted] are added to [redacted] to allow reaction. Water is added to stop the reaction, 2-propanol and [redacted] are then added to this solution to allow reaction. The reaction mixture is concentrated and its pH is then adjusted with a mixed solution of sodium hydrogen carbonate and sodium carbonate. The organic layer is separated, concentrated, and purified by silica gel column chromatography. The chromatography eluate is concentrated and its pH is adjusted with a mixed solution of sodium hydrogen carbonate and sodium carbonate. The organic layer is then separated and concentrated to obtain [redacted].

Step [redacted]: Synthesis of eribulin mesilate

The mixture of [redacted] is added to [redacted]. The resulting solution is concentrated and the residue is dissolved in a DCM/*n*-pentane mixture. This solution is dripped into *n*-pentane, and the resulting precipitate is filtered and dried under reduced pressure to obtain eribulin mesilate. The obtained eribulin mesilate is collected in polytetrafluoroethylene containers, which are then closed with polytetrafluoroethylene lids and placed in aluminum-laminated bags. The bags are then heat-sealed and labeled.

(b) Controls of the critical steps and intermediates

A total of [redacted] steps, namely, Step [redacted], Step [redacted], Step [redacted], Step [redacted], Step [redacted], Step [redacted], and Step [redacted] were defined as critical steps. Critical parameters were temperature conditions during reaction, stop of reaction, and concentration in all steps; the composition and volume of solvents for column purification; and [redacted].

Critical intermediates were the intermediates in [redacted] of the [redacted] critical steps, excluding the final step to obtain the drug substance (Step [redacted]), namely, [redacted] (Step [redacted]), [redacted] (Step [redacted]), [redacted] (Step [redacted]), [redacted] (Step [redacted]), [redacted] (Step [redacted]), and [redacted] (Step [redacted]). These critical intermediates undergo identification testing by liquid chromatography ([redacted]) and impurity testing, and only those that meet process control standards are used in the subsequent step. Residual solvents are controlled in [redacted] (Step [redacted]) and [redacted] (Step [redacted]).

(c) Controls of the starting materials

Among the carbons forming the skeleton of eribulin mesilate, [redacted] to [redacted] are derived from Starting Material 1 and [redacted] to [redacted] from Starting Material 2.

Staring Material 1 is synthesized from commercially available [redacted] and is used as [redacted]. Control parameters of Starting Material 1 were description, identification (IR, liquid chromatography), water content, related substances, and assay (content). Starting Material 2 is synthesized as a single stereoisomer from commercially available [redacted] and [redacted]. Control parameters of Starting Material 2 were description, identification (IR, normal-phase liquid chromatography), related substances by [redacted] types of liquid chromatography ([redacted], [redacted]), assay (normal-phase liquid chromatography), water content, and residual solvents (gas chromatography).

2.A.(1).3) Controls of the drug substance

The proposed specifications for the drug substance were content (eribulin mesilate, methanesulfonic acid), description (appearance), identification (IR), optical rotation, purity (residual metals [inductively coupled plasma atomic emission spectrophotometry]), related substances (liquid chromatography), residual solvents (gas chromatography), water content, and assay (liquid chromatography).

2.A.(1).4) Stability of the drug substance

Stability study data on the drug substance were submitted. The data were obtained from 3 primary stability batches manufactured by Eisai Co., Ltd./[redacted] ([redacted]) and 3 commitment batches manufactured by Eisai Co., Ltd. The stability studies were conducted under the following conditions:

Testing conditions for stability studies

Batch	Study	Storage condition			Storage period
		Temperature	Humidity	Storage container	
Primary	Long-term	−65°C	–	Polytetrafluoroethylene bottle	24 months
		−20°C	–		24 months
		5°C	–		12 months
	Short-term	25°C	60% RH		1 month
Commitment	Stress (temperature)	60°C	–	Glass bottle	1 month
	Stress (humidity)	30°C	75% RH	Opaque glass bottle	1 month
	Stress (light)	–	–	Petri dish (with a quartz lid)	Overall illumination of 1.3 Mlx·hr, an integrated near ultraviolet energy of 540 W·h/m^2
	Long-term	−65°C	–	Polytetrafluoroethylene bottle	24 months (2 batches), 18 months (3 batches)
		−20°C	–		24 months (2 batches), 18 months (3 batches)
		5°C	–		12 months (1 batch), 1 month (2 batches)

In the long-term testing (−65°C, −20°C, and 5°C) of primary batches, the quality of drug substance was not affected at −65°C or −20°C. At 5°C, the amount of related substances increased (by up to [redacted]% as a total amount of related substances) while the content of eribulin mesilate decreased (by up to [redacted]%).

In the long-term testing (−65°C, −20°C, and 5°C) of commitment batches, the quality of drug substance was not affected under any storage condition.

In the short-term testing (25°C) of primary batches, the amount of related substances increased (by up to [redacted]% as a total amount of related substances) while the content of eribulin mesilate decreased (by up to [redacted]%).

In the stress testing (temperature) of commitment batches, the amount of related substances increased (by up to [redacted]% as a total amount of related substances) while the content of eribulin mesilate decreased (by up to [redacted]%).

In the stress testing (humidity) of commitment batches, the quality of drug substance was not affected.

In the stress testing (light) of commitment batches, the amount of related substances increased (by up to [redacted]% as a total amount of related substances) while the content of eribulin mesilate decreased (by up to [redacted]%).

Based on the above data, a retest period of [redacted] months was proposed for eribulin mesilate when stored at −65°C in a polytetrafluoroethylene bottle. The applicant plans to continue long-term studies for up to [redacted] years with primary batches and up to [redacted] years with commitment batches.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product

Halaven Injection 1 mg (the drug product) is an aqueous solution for injection containing 1.0 mg of eribulin mesilate per vial as the active ingredient. The drug product may be administered undiluted or diluted with saline. The formulation of the drug product is shown below.

Formulation of Halaven Injection 1 mg

Ingredient	Function	Quantity per vial
Eribulin mesilate	Active ingredient	1.0 mg
Anhydrous ethanol	Solvent	0.10 mL
Hydrochloric acid	pH adjuster	Appropriate quantity
Sodium hydroxide	pH adjuster	Appropriate quantity
Water for injection	Solvent	Appropriate quantity
Total		2.0 mL

2.A.(2).2) Pharmaceutical development

(a) Manufacturing process

In the development of the drug product, the main parameters that affect the stability of the drug product were considered to be [redacted] and [redacted] because eribulin mesilate [redacted]. As a result, [redacted] that warrants the stability of the drug product was determined to be [redacted] to [redacted]. Sterilization by filtration is performed to prevent degradation by [redacted].

(b) Compatibility with diluents

Compatibility of eribulin mesilate with 5% glucose injection or saline was investigated at concentrations ranging from [redacted] to [redacted] mg/mL. While the drug product was compatible with saline, a reaction product (with an unidentified chemical structure) was detected in the drug product diluted with 5% glucose injection.

(c) Compatibility with dosage devices

Undiluted drug product was compatible with polypropylene syringes.

When the drug product was diluted with saline to [redacted] mg/mL and filled in polypropylene syringes, approximately [redacted]% of [redacted] was detected when stored under refrigeration (2°C-8°C) and approximately [redacted]% of [redacted] at room temperature (20°C-25°C). In the drug product diluted to [redacted] mg/mL, no [redacted] was detected either at room temperature or under refrigeration. The amount of related substances did not increase in the refrigerated drug product, but the total amount of related substances increased by up to [redacted]% in the drug product stored at room temperature.

The drug product was diluted with saline and filled in polypropylene/polyethylene infusion bags or in [redacted] (connection material, polyvinyl chloride). In the drug product diluted to [redacted] mg/mL, up to approximately [redacted]% of [redacted] was detected when stored in polypropylene/polyethylene infusion bags and approximately [redacted]% in [redacted]. In the drug product diluted to [redacted]

mg/mL, no [redacted] was detected in either infusion bag. The total amount of related substances increased by up to [redacted]% in the drug product stored at room temperature.

Accordingly, the package insert will include the following precautionary advice: 1) the drug product should not be diluted with 5% glucose injection; and 2) the drug product should be used immediately after preparation.

2.A.(2).3) Manufacturing process

The drug product is manufactured by the following 12 steps. Steps [redacted] through [redacted] are performed at [redacted], and Steps [redacted] through [redacted] at [redacted]. Steps [redacted] through [redacted] were defined as critical process steps.

Step 1: Dissolution of the drug substance

Anhydrous ethanol is poured into a solution tank. Eribulin mesilate is added and stirred to dissolve. Injection water is poured into a diluent preparation tank. The ethanol solution containing eribulin mesilate is then transferred into the diluent preparation tank. Injection water ([redacted]% of the total mass) is added and stirred.

Step 2: pH adjustment/constant volume

The pH of the drug solution prepared in Step 1 is adjusted to [redacted] to [redacted]. Injection water is added and stirred.

Step 3: Sterilization by filtration

The drug solution produced in Step 2 is filtrated through [redacted] ([redacted] μm in pore size). It is then sterile-filtrated through a dual-coupled [redacted] ([redacted] μm in pore size).

Step 4: Aseptic filling/stoppering

The drug solution sterile-filtered in Step 3 is aseptically filled in [redacted] mL [redacted]. The vials are then stoppered with [redacted].

Step 5: Sealing

The vials are sealed with [redacted] and the outer surface of the vials is washed.

Step 6: Visual inspection

Vials sealed and washed in Step 5 are visually inspected. Defective vials are rejected.

Step 7: Packaging/labeling

Vials are packed in bulk.

Step 8: Testing

Tests are performed.

Step 9: Visual inspection

Vials are visually inspected. Defective vials are rejected.

Step 10: Packaging/labeling

Secondary packaging is performed.

Step 11: Storage

Packaged products are stored.

Step 12: Testing

Release test is performed.

2.A.(2).4) Control of the drug product

The proposed specifications for the drug product consist of content, description (appearance), identification (thin-layer chromatography, liquid chromatography), pH, purity (related substances), endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, and assay (liquid chromatography).

2.A.(2).5) Stability of the drug product

Stability study data on the drug product were submitted. The data were obtained from the following batches: 3 primary batches using the drug substance manufactured by Eisai Co., Ltd./[redacted] ([redacted]); sample batches for supplemental stability tests using the drug substance manufactured by ERI (currently, Eisai Inc.)/[redacted]; and sample batches for additional stability tests using the drug substance manufactured by Eisai Co., Ltd., the commercial production site.

The testing conditions for the stability studies conducted are shown below. The applicant plans to conduct long-term testing of the drug product for up to 48 months.

Testing conditions for stability studies

Batch	Test	Storage condition			Storage period
		Temperature	Humidity	Other	
Primary	Long-term	25°C	60% RH	Dark; upright or inverted	36 months
	Medium-term	30°C	65% RH		12 months
	Accelerated	40°C	75% RH		6 months
	Stress (light)	–	–	Irradiation with ID 65 lamp; upright, inverted, or horizontal	250 W/m^2 (illumination, approx. 55 klx; near ultraviolet energy, approx. 22.5 W/m^2) × 24 hours
	Thermal cycling	–	–	Upright and inverted	(−25°C to −10°C for 2 days and 40°C/75% RH for 2 days) × 3 cycles
Additional stability test [redacted] (manufacturing scale, [redacted] L)	Long-term	25°C	60% RH	Dark; upright or inverted	24 months
	Medium-term	30°C	65% RH		12 months
	Accelerated	40°C	75% RH		6 months
Additional stability test [redacted] (manufacturing scale, [redacted] L)	Long-term	25°C	60% RH	Dark; upright or inverted	18 months
	Medium-term	30°C	65% RH		12 months
	Accelerated	40°C	75% RH		6 months
Additional stability test [redacted] (manufacturing scale, [redacted] L)	Long-term	25°C	60% RH	Dark; upright or inverted	1 month
	Medium-term	30°C	65% RH		1 month
	Accelerated	40°C	75% RH		1 month
Supplemental stability tests	Long-term	25°C	60% RH	Dark; inverted	48 months
	Accelerated	40°C	75% RH		6 months

(a) Primary batches

The long-term and medium-term tests showed increased pH (by approximately [redacted] from baseline), increased total amount of related substances (by up to approximately [redacted]% from baseline), and decreased content (by up to approximately [redacted]% from baseline). However, there were no changes posing a quality problem throughout the storage periods. There was little difference in stability between the drug product stored upright and that stored inverted.

The accelerated tests showed increased pH (by approximately [redacted] from baseline), increased total amount of related substances (by up to approximately [redacted]% from baseline), and decreased content (by up to approximately [redacted]% from baseline). However, there were no changes posing a quality problem throughout the storage periods. There was little difference in stability between the drug product stored upright and that inverted.

The stress test (light) showed no degradation of the drug product caused by light.

The thermal cycling test showed increased pH (by approximately [redacted] from baseline), increased total amount of related substances (by up to approximately [redacted]% from baseline), and decreased content (by up to approximately [redacted]% from baseline). However, there were no changes posing a quality problem throughout the storage periods. There was little difference in stability between the drug product stored upright and that stored inverted.

(b) Additional stability test 1

The long-term, medium-term, and accelerated tests showed increased pH (by approximately [redacted] from baseline), increased total amount of related substances (by up to approximately [redacted]%, [redacted]%, and [redacted]%, respectively, from baseline), and decreased content (by up to approximately [redacted]%, [redacted]%, and [redacted]%, respectively, from baseline). However, there were no changes posing a quality problem throughout the storage periods. There was little difference in stability between the drug product stored upright and that stored inverted.

(c) Additional stability test 2

The long-term, medium-term, and accelerated tests showed increased pH (by approximately [redacted], [redacted], and [redacted], respectively, from baseline), increased total amount of related substances (by up to approximately [redacted]%, [redacted]%, and [redacted]%, respectively, from baseline), and decreased content (by up to approximately [redacted]%, [redacted]%, and [redacted]%, respectively, from baseline). However, there were no changes posing a quality problem throughout the storage periods. There was little difference in stability between the drug product stored upright and that stored inverted.

(d) Additional stability test 3

The long-term, medium-term, and accelerated tests showed increased pH (by approximately [redacted] from baseline), increased total amount of related substances (by up to approximately [redacted]%, [redacted]%, and [redacted]%, respectively, from baseline), and decreased content (by up to [redacted]% from baseline). However, there were no changes posing a quality problem throughout the storage periods. There was little difference in stability between the drug product stored upright and that stored inverted.

(e) Supplemental stability tests

The long-term test showed increased pH (by approximately [redacted] from baseline) and decreased content (by up to [redacted]% from baseline). However, there were no changes posing a quality problem throughout the storage period.

The accelerated test showed increased pH (by approximately [redacted] from baseline), increased total amount of related substances (by up to [redacted]% from baseline), and decreased content (by up to [redacted]% from baseline). However, there were no changes posing a quality problem throughout the storage period.

Based on the above, a shelf life of 48 months was proposed for the drug product when stored at room temperature in accordance with the “Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau).

2.A.(3) Reference material

2.A.(3).1) Purification

Eribulin mesilate is left at approximately [redacted]°C and [redacted] ± [redacted]% RH to remove [redacted], and is then dried at approximately [redacted]°C under reduced pressure for [redacted].

2.A.(3).2) Specifications

The proposed specifications for the reference material of eribulin mesilate include description (appearance), identification (IR, nuclear magnetic resonance spectroscopy [^{1}H-NMR, ^{13}C-NMR], MS), optical rotation, purity (related substances, residual solvents, residue on ignition), water content, assay (methanesulfonic acid [liquid chromatography]), and purity (eribulin mesilate).

2.B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA concluded that the quality of the drug product is adequately controlled.

Starting materials

Several intermediates are produced during the synthesis of the drug substance from commercially-available raw materials. Among these intermediates, Starting Materials 1 and 2 were defined by the applicant as starting materials of the drug substance, because Starting Materials 1 and 2 were considered most appropriate to ensure the quality of the drug substance. PMDA asked the applicant to explain the rationale for the definition.

The applicant's response based on the Guidelines on GMP for Drug Substances (PFSB Notification No. 1200 dated November 2, 2001) and the Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc., under the Revised Pharmaceutical Affairs Law (PFSB/ELD Notification No. 0210001 dated February 10, 2005):

(a) The drug substance is a large cyclic compound with 19 asymmetric carbons. This basic skeleton is formed by the binding of Starting Material 1 with [redacted] asymmetric carbons and Starting Material 2 with [redacted] asymmetric carbons. The chemical structure and configuration of each starting material are determined by a single-crystal X-ray structure analysis, NMR, MS, and other techniques.

(b) The drug substance is synthesized from the starting materials through [redacted] steps. For the purpose of impurity control, [redacted] times of extraction, [redacted] times of column purification, [redacted] times of crystallization, and [redacted] times of precipitation are performed during these steps. Because no impurities derived from the impurities of each starting material have been detected, Starting Materials 1 and 2 assure the quality of the drug substance.

(c) Starting Material 1

- [redacted] binds to Starting Material 2, and has [redacted] and [redacted]. Starting Material 1 is a synthetic material for [redacted] and can be stored for a long time in [redacted].
- The quality of Starting Material 1 is adequately controlled by the following specifications: description, identification (IR, liquid chromatography [HPLC]), related substances (liquid chromatography), water content, and assay.
- Starting Material 1 is expected to be contaminated by [redacted] types of related substances. These substances, however, can be separated and detected by tests for Starting Material 1 related substances (liquid chromatography) and are, therefore, controllable by the specifications.
- The specifications require the amount of each related substance in Starting Material 1 to be ≤[redacted]%. No impurities derived from Starting Material 1 were detected in the drug substance.
- In Step [redacted], residues of Starting Material 1 from the previous step are controlled to be ≤[redacted]% by the specifications. Therefore, such residues are unlikely to affect the quality of the drug substance.

(d) Starting Material 2

- Starting Material 2 is separated and purified as [redacted] and is chemically stable. The amount of related substances can be [redacted] by [redacted].
- The quality of Starting Material 2 is adequately controlled by the following specifications: description, identification (IR, HPLC), related substances (liquid chromatography), water content, residual solvents, and assay.
- Starting Material 2 is expected to be contaminated by [redacted] types of related substances. These substances, however, can be detected by related substance tests (liquid chromatography) and are therefore controllable as per the specifications.
- Of the related substances of Starting Material 2, [redacted] types of related substances and other related substances are controlled to be ≤[redacted]% by the specifications. Therefore, such related substances are unlikely to affect the quality of the drug substance.
- [redacted] types of related substances of Starting Material 2 are controlled to be >[redacted]%. The derivatives of these related substances, however, are controlled to be ≤[redacted]% in the GMP process by specifications for intermediates. Therefore, these related substances do not affect the quality of the drug substance.
- In Step [redacted], a derivative ([redacted]) of Starting Material 2 is controlled to be ≤[redacted]% by the specifications, to control residues of Starting Material 2 in subsequent steps. Therefore, Starting Material 2 does not affect the quality of the drug substance.

Given these facts, of all intermediates produced during the synthesis of the drug substance from commercially-available raw materials, Starting Materials 1 and 2 are the most appropriate starting materials that assure the quality of the drug substance.

The PMDA accepted the applicant's explanation.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Inhibition of tumor cell proliferation

***In vitro*:**

(a) Inhibition of cell proliferation in a human breast cancer cell line (Study CAIVT0101)

The antiproliferative effect of eribulin mesilate (0.03-1000 nmol/L) on the MDA-MB-435 human breast cancer cell line was evaluated. Paclitaxel (PTX) and vinblastine sulfate (VLB) were used as positive controls. The IC_{50} values of eribulin mesilate, PTX, and VLB against the MDA-MB-435 cell line were 0.51, 4.94, and 0.71 nmol/L, respectively. Eribulin mesilate inhibited the proliferation of the MDA-MB-435 cell line in a dose-dependent manner, and the IC_{50} of eribulin mesilate was not markedly different from that of PTX or VLB. According to the applicant, these results demonstrated that eribulin mesilate and the positive controls had similar antiproliferative effect against breast cancer cells.

(b) Inhibition of cell proliferation by eribulin mesilate when combined with docetaxel (Study SA030105)

The antiproliferative effects of eribulin mesilate or docetaxel hydrate (DTX) alone and eribulin mesilate combined with DTX were examined on the MDA-MB-231, MDA-MB-435, MDA-MB-468, and HCC1806 human breast cancer cell lines (see the table below). The IC_{50} values against these cell lines ranged from 0.2 to 1 nmol/L for eribulin mesilate alone and 0.4 to 2.5 nmol/L for DTX alone. The applicant explained that eribulin mesilate combined with DTX exerted an additive effect or a mild antagonistic effect on the MDA-MB-468 cell line and an additive effect on the other 3 cell lines based on the combination indices* (CI) (CI values at ED_{50} and mean CI values).

*A method developed for the quantitative evaluation of drug interactions (additive, synergistic, and antagonistic effects) ([Manual and Software] Cambridge: Biosoft; 1987. In: *Synergism and Antagonism in Chemotherapy*. San Diego: Academic Press; 1991).

Anti-proliferative effect of eribulin mesilate combined with docetaxel hydrate (*in vitro*)

Cell line	IC_{50} (nmol/L)		Combination effect	
	Eribulin mesilate	DTX	CI at ED_{50}	Mean CI
MDA-MB-231	1	2.5	Additive effect	Additive effect
MDA-MB-435	0.2	0.6	Additive effect	Additive effect
MDA-MB-468	0.3	2	Additive effect	Mild antagonistic effect
HCC1806	0.3	0.4	Additive effect	Additive effect

The antiproliferative effect of eribulin mesilate on human cancer cell lines derived from various malignancies, including colorectal and prostate cancers (13 cell lines for eribulin mesilate alone and 4 cell lines for eribulin mesilate combined with carboplatin), were examined in *in vitro* studies. The results of these studies are included in the new drug application data, but are omitted from this review report because the cancer types examined in the studies were different from the proposed indication of eribulin mesilate.

***In vivo*:**

(a) Inhibition of tumor growth in a human breast cancer cell line (Study ERI-14)

The antiproliferative effect of eribulin mesilate was evaluated in female athymic mice bearing a subcutaneous xenograft of the MDA-MB-435 cell line. From the day when the pre-specified tumor weight was achieved (Day 14) after xenografting, eribulin mesilate was administered intravenously to the mice once daily at any of the following dosage regimens to make the total dose of 4.5 or 9 mg/kg. The tumor weight at Day 56 and the proportion of surviving animals achieving a complete regression of tumors at Day 157 were calculated (n = 10/group).

Dosing regimens of eribulin mesilate

i) 0.9 or 1.8 mg/kg for 5 consecutive days (hereinafter referred to as Q1D × 5)
ii) 0.5 or 1 mg/kg 3 times weekly at 2-day intervals for 3 weeks (hereinafter referred to as Q2D × 3)
iii) 1.5 or 3 mg/kg 3 times at 4-day intervals (hereinafter referred to as Q4D × 3)
iv) 1.5 or 3 mg/kg 3 times at 7-day intervals (hereinafter referred to as Q7D × 3)

In the Q1D × 5 group receiving a total dose of 4.5 mg/kg and all groups receiving a total dose of 9 mg/kg, mortalities by Day 122 were 70% to 100% despite decreased tumor weight. This toxicity (mortalities) precluded the evaluation of these doses. Meanwhile, in the Q2D × 3, Q4D × 3, and Q7D × 3 groups receiving a total dose of 4.5 mg/kg, the mean maximum weight loss rates in athymic mice were 0%, 14%, and 9%, respectively; the applicant explained that the results demonstrated tolerability of these regimens.

Tumor weight ± standard error at Day 56 was 2696 ± 445 mg in the vehicle control group, 0 mg (tumors unidentifiable in any surviving mice) in the Q2D × 3 and Q4D × 3 groups receiving a total dose of 4.5 mg/kg, and 12 ± 12 mg in the Q7D × 3 group receiving a total dose of 4.5 mg/kg. The proportion of surviving animals achieving a complete regression of tumors at Day 157 was 0% in the control group, 80% in the Q2D × 3 group, 70% in the Q4D × 3 group, and 70% in the Q7D × 3 group. The applicant explained the results demonstrated the efficacy of eribulin mesilate.

The above results failed to determine the optimal dosage regimen of eribulin mesilate. However, the applicant explains that eribulin mesilate is well tolerated and has an antiproliferative effect on breast cancer cell when administered intravenously at appropriate intervals.

(b) Inhibition of tumor growth by eribulin mesilate when combined with other antitumor drugs (Studies ERI-118, ERI-119, and ERI-30)

The following investigations were conducted to evaluate antiproliferative effect of eribulin mesilate in combination with other antitumor drugs. The results of these investigations are presented only briefly,

because eribulin mesilate is not expected to be used with other antitumor drugs for the proposed indication.

- The antiproliferative effects of eribulin mesilate with capecitabine were evaluated in female athymic mice bearing a subcutaneous xenograft of tumor tissue sections derived from the MX-1 human breast cancer cell line. From the day when the pre-specified tumor weight was achieved after xenografting, eribulin mesilate (intravenous dose of 0.2, 0.4, 0.8, or 1.6 mg/kg given at the Q4D × 4 regimen) or capecitabine (oral dose of 220, 330, 500, or 750 mg/kg at the Q1D × 14 regimen) was administered to the mice to examine a time needed to observe a 16-fold increase in tumor weight (n = 10/group). Eribulin mesilate alone at 0.2, 0.4, 0.8, or 1.6 mg/kg delayed tumor growth by 2.5, 22.5, >59.6, and >59.6 days, respectively, as compared with the vehicle control. The results demonstrated that eribulin mesilate ≥0.4 mg/kg significantly inhibits tumor growth. Eribulin mesilate 0.2 or 0.4 mg/kg in combination with capecitabine 330 or 500 mg/kg delayed tumor growth as compared with eribulin mesilate or capecitabine alone. The applicant considers that the result shows enhanced antiproliferative action of eribulin mesilate when combined with capecitabine. A similar investigation was performed in the UISO-BCA-1 human breast cancer cell line, and the results also showed enhanced antiproliferative action of eribulin mesilate when combined with capecitabine.
- The antiproliferative effects of eribulin mesilate combined with doxorubicin hydrochloride (DXR) were evaluated in female athymic mice bearing a subcutaneous xenograft of tumor tissue sections derived from the MDA-MB-435 cell line. From the day when the pre-specified tumor weight was achieved after xenografting, eribulin mesilate (0.12, 0.18, 0.27, or 0.4 mg/kg) or DXR (3.59, 5.36, or 8 mg/kg) was administered intravenously at the Q4D × 3 regimen to the mice to examine the time needed to observe a 4-fold increase in tumor weight (n = 10/group). Eribulin mesilate alone at 0.12, 0.18, 0.27, or 0.4 mg/kg delayed tumor growth by 14.5, 28.9, 56.8, and 46.2 days, respectively, as compared with the vehicle control. However, eribulin mesilate plus DXR did not significantly delay tumor growth as compared with eribulin mesilate alone. The applicant considered that these results showed no enhanced antiproliferative action of eribulin mesilate when combined with DXR.

3.(i).A.(1).2) Mechanism of action

(a) Effect of eribulin mesilate on the cell cycle (Study CAIVT0100)

The effect of eribulin mesilate on the cell cycle was examined by flow cytometry using the U937 human lymphoma cell line. Treatment with 100 nmol/L of eribulin mesilate led to increases in the proportions of cells in the G2/M phase and cells with decreased DNA replication (hypodiploid cells).

According to the applicant, these results suggest that eribulin mesilate induces G2/M cell cycle arrest (an effect characteristic of tubulin-targeting antitumor drugs) and apoptosis.

(b) Effect of eribulin mesilate on tubulin polymerization (Study CAIVT0103)

The inhibitory effect of eribulin mesilate on tubulin polymerization was evaluated *in vitro* using tubulin purified from bovine brain (hereinafter referred to as purified tubulin). Both eribulin mesilate and VLB, a positive control, inhibited tubulin polymerization in a dose-dependent manner. The IC_{50} values of eribulin mesilate and VLB were 15.3 and 3.08 μmol/L, respectively, as measured by the maximum tubulin polymerization rate, and 39.2 and 4.76 μmol/L, respectively, as measured by the amount of tubulin polymerization.

According to the applicant, these results suggest that eribulin mesilate has a lower inhibitory effect on tubulin polymerization than VLB.

3.(i).A.(1).3) Effect of eribulin mesilate on drug resistant cell lines (Studies CAIVT0102, CAIVT0105, and CAIVT0106)

The following investigations were conducted to evaluate antiproliferative effect of eribulin mesilate on drug-resistant cancer cell lines.

- The antiproliferative effects of eribulin mesilate, PTX, and VLB on the PTX-resistant human ovarian cancer cell lines with β-tubulin mutations (1A9PTX10 and 1A9PTX22) and their parent cell line (A2780/1A9) were evaluated. The resistance ratios (IC_{50} against each PTX-resistant cell line/IC_{50} against the parent cell line) were calculated. For the 1A9PTX10 cell line, the resistance ratio was 1.33 (eribulin mesilate), 15.3 (PTX), and 1.25 (VLB). For the 1A9PTX22 cell line, the resistance ratio was 1.31 (eribulin mesilate), 18.9 (PTX), and 1.27 (VLB).
- The antiproliferative effects of eribulin mesilate, PTX, VLB, and methotrexate (MTX) on the multidrug-resistant human uterine sarcoma cell line MES-SA/Dx5-Rx1 overexpressing P-glycoprotein (P-gp) and its parent cell line MES-SA were evaluated. The resistant ratio (IC_{50} against the MES-SA/Dx5-Rx1 cell line/IC_{50} against the MES-SA cell line) was 2670 (eribulin mesilate), 425 (PTX), 180 (VLB), and 1 (MTX) when each drug was used alone, and 42.7 (eribulin mesilate), 5.2 (PTX), 3.3 (VLB), and 0.9 (MTX) when each drug was used with verapamil, a P-gp inhibitor.

The applicant considers the results suggest that the antiproliferative effects of eribulin mesilate may be reduced on P-gp-expressing cells but, similarly to VLB, remain unchanged on taxane-resistant cells with β-tubulin mutations.

3.(i).A.(2) Safety pharmacology

3.(i).A.(2).1) Effects on the cardiovascular system (Studies [redacted]H03-001, [redacted]P03-002, and [redacted]T03-001)

The effect of eribulin mesilate 30 μmol/L on the potassium ion current (I_{Kr}) was evaluated by the patch-clamp method in the human ether-a-go-go-related gene (hERG)-transfected HEK293 human fetal kidney cell line. The mean hERG tail current inhibition rate was 23.2% for eribulin mesilate and 16.4%

for the vehicle control (0.1% ethanol solution), showing no significant difference between eribulin mesilate and the vehicle control.

The effects of eribulin mesilate 1, 10, or 30 μmol/L on the cardiac action potential were evaluated in canine Purkinje's fibers. Eribulin mesilate at any concentration had no effects on any action potential parameters.

The effects of eribulin mesilate on the heart rate, blood pressure, and electrocardiogram (ECG) were evaluated in dogs (n = 3/sex) given a single intravenous infusion of eribulin mesilate at 0.01 or 0.04 mg/kg over 60 minutes. The eribulin mesilate 0.01 mg/kg group showed no effects on the heart rate, blood pressure, or ECG. The eribulin mesilate 0.04 mg/kg group showed transient decreases in blood pressure and heart rate and prolonged RR interval. Compared with male animals given the vehicle control, male animals given 0.04 mg/kg showed decreased blood pressure by 18% at 60 minutes post-dose and prolonged RR intervals by 14% and 45% at 30 and 60 minutes post-dose, respectively.

The applicant explained that eribulin mesilate has practically no effect on the cardiovascular system in clinical use for the following reasons: (a) The observed transient decreases in blood pressure and heart rate and prolonged RR intervals were minor changes in the mean values, but the over-time changes seen in individual animals were within the normal range. (b) In a 6-month repeated intravenous dose toxicity study in dogs, no effects were observed on the heart rate or ECG parameters following 3 doses of eribulin mesilate 0.0045, 0.015, or 0.045 mg/kg administered at 7-day intervals [see 3.(iii).A.(2) Repeat-dose toxicity].

3.(i).A.(2).2) Effects on the central nervous system (Study [redacted]I03-003)

A single dose of eribulin mesilate 0.1 or 0.25 mg/kg was administered intravenously to male rats (n = 6/group) to study the effects of eribulin mesilate on clinical signs and behaviors by the Irwin test. There were no changes caused by eribulin mesilate.

3.(i).A.(2).3) Effects on the respiratory system (Study [redacted]R03-003)

Following a single intravenous dose of eribulin mesilate 0.1 or 0.25 mg/kg administered to male rats (n = 6/group), the respiratory rate and tidal volume were measured using systemic plethysmography. The measured values showed no effects of eribulin mesilate on these parameters.

3.(i).A.(2).4) Effects on the peripheral nervous system (Study PPC20[redacted]-01)

Eribulin mesilate 0.44, 0.88, 1.31, or 1.75 (equivalent to maximum tolerated dose [MTD]) mg/kg or PTX 7.5, 15, 22.5, or 30 (equivalent to MTD) mg/kg was intravenously administered 3 times weekly for 2 weeks to female mice (n = 10/group) to examine any peripheral nerve disorder caused by eribulin mesilate. At 24 hours after the final dose, the speed and amplitude of neurotransmission in the tail nerve

and the digital nerve were measured. The sciatic nerve and the dorsal root ganglion (DRG) were removed from some animals in each group for histological examination.

After stimulation (0.02-0.05 milliseconds, 3-6 times) of the tail and digital nerves, the speed and amplitude of neurotransmission were measured. As compared with the vehicle control group, none of the eribulin mesilate groups showed significant differences in the speed or amplitude of neurotransmission in the tail or digital nerve. The PTX groups showed the following findings:
(a) In the tail nerve, the speed and amplitude of neurotransmission decreased in a dose-dependent manner. As compared with the vehicle control group, the 30 mg/kg group showed a significant decrease in the speed of neurotransmission (by 18%), and the 22.5 and 30 mg/kg groups showed a significant decrease in the amplitude of neurotransmission (by 63.5% and 48.8%, respectively).
(b) In the digital nerve, the speed of neurotransmission tended to decrease (without significant difference from the vehicle control group). In the 22.5 and 30 mg/kg groups, the amplitude of neurotransmission in the digital nerve decreased significantly (62.8% and 35.2%, respectively) as compared with the vehicle control group. Histological findings in the ≥0.88 mg/kg eribulin mesilate groups were vacuolated nerve cells in the DRG and abnormal changes such as axonal degeneration in the sciatic nerve. Both findings were milder than those in the PTX groups.

Based on the above, the applicant explained that the effects of eribulin mesilate on the peripheral nervous system are small as compared with PTX given at a dose of the same MTD ratio.

3.(i).B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA concluded that eribulin mesilate is expected to be effective in the treatment of breast cancer.

3.(i).B.(1) Mechanism of action of eribulin mesilate

Based on the submitted data and the following published papers, the applicant explained that eribulin mesilate inhibits tubulin polymerization to suppress the growth of microtubules, thereby disrupting normal spindle formation; this induces G2/M phase cell cycle arrest and results in apoptotic cell death.

- Affinity chromatography demonstrated a direct binding of a biotin-labeled derivative of eribulin mesilate to purified tubulin (*Cancer Res.* 2001;61:1013-21).
- In a biochemical study with purified tubulin, eribulin mesilate inhibited tubulin polymerization [see "3.(i).A.(1).2) (b) Effect of eribulin mesilate on tubulin polymerization"] (*Cancer Res*. 2001;61:1013-21).
- In a biochemical study with purified tubulin and an *in vitro* study with the MCF-7 human breast cancer cell line, eribulin mesilate inhibited microtubule growth only at the plus end without affecting microtubule shrinkage at the plus end or microtubule growth or shrinkage at the minus end (*Mol Cancer Ther.* 2005;4:1086-95. *Biochem*. 2010;49:1331-7).

- In *in vitro* studies with the MCF-7 cell line and the DU145 human prostate cancer cell line, chromosome images suggested the disruption of normal spindle structure and mitotic metaphase arrest (*Mol Cancer Ther.* 2005;4:1086-95. *Cancer Res.* 2001;61:1013-21).
- In an *in vitro* study with the U937 and the LNCaP cell lines, the proportions of cells in the G2/M phase and hypodiploid cells increased [see "3.(i).A.(1).2) (a) Effect of eribulin mesilate on cell cycle"] (*Cancer Res.* 2004;64:5760-6).
- Eribulin mesilate has been shown to induce apoptosis in a time-dependent manner by (1) an *in vitro* study with the U937 and the LNCaP cell lines showing increased Bcl-2 phosphorylation and activation of caspase-3 and caspase-9; (2) flow cytometry with the U937 cell line showing a color shift on acridine orange/ethidium bromide staining and annexin V positivity, both of which occur in apoptosis (*Cancer Res*. 2004;64:5760-6).

The applicant's explanation based on the following published literature:
Eribulin mesilate inhibits microtubule growth at the plus end only, in contrast to existing tubulin-targeting drugs such as PTX, VLB, and epothilone B.

- In a biochemical study with purified tubulin, VLB inhibited microtubule growth and shrinkage at the plus end but not at the minus end (*J Biol Chem*. 1996;271:29807-12).
- In an *in vitro* study with the MCF-7 cell line, PTX and epothilone B inhibited both microtubule growth and shrinkage (*Cancer Res.* 2003;63:6026-31).

PMDA's view:
The applicant's discussions on the mechanism of action of eribulin mesilate are acceptable. However, eribulin mesilate has not been shown to have a pharmacologically novel mechanism of tumor growth inhibition, for the following reasons:

- In contrast to other tubulin-targeting drugs, eribulin mesilate predominantly inhibits microtubule growth at the plus end. This is a molecular level-characteristic of eribulin mesilate. However, the clinical significance of this characteristic is being investigated and remains unclear at present.
- Eribulin mesilate has a different mechanism of tubulin polymerization inhibition from other tubulin-targeting drugs. At the same time, eribulin mesilate suppresses tumor growth through microtubule growth inhibition, disruption of normal spindle formation, G2/M cell cycle arrest, and apoptosis induction, as with other tubulin-targeting drugs.

3.(i).B.(2) Efficacy of eribulin mesilate

The proposed indication of eribulin mesilate is breast cancer that has worsened or recurred after treatment with chemotherapy including a taxane, which also targets tubulin. PMDA asked the applicant to explain the effect of eribulin mesilate on taxane-resistant cells.

The applicant's response:

Currently available data implicate the following are involved in the development of cellular resistance to taxanes: (i) overexpression of P-gp as a drug efflux pump; (ii) overexpression of β-tubulin isotypes; and (iii) β-tubulin isotype mutation.

(i) The overexpression of P-gp is suggested to be involved in the development of resistance to eribulin mesilate [see "3.(i).B.(3) Mechanism of resistance acquisition to eribulin mesilate"]. P-gp-overexpressing cells are assumed to be resistant not only to taxanes but also to eribulin mesilate. However, no definite conclusions have been drawn as to how overexpressed P-gp contributes to the development of resistance to anticancer drugs in clinical settings.

(ii), (iii) The exact eribulin-binding site on tubulin is currently unknown, but the following reviews and published literature indicate that, similarly to vinca alkaloids, eribulin acts on tubulin differently (i.e., binds to a different site) from taxanes that bind to β-tubulin. Therefore, the antiproliferative effect of eribulin mesilate is considered unaffected by the mutation or quantitative change of β-tubulin isotypes.

- Eribulin is assumed to bind to the vinca domain (the binding site for VLB) or its neighboring domain (*Biochem*. 2010;49:1331-7. *Mol Pharmacol*. 2006;70:1866-75).
- The antiproliferative effect of eribulin mesilate was not reduced on taxane-resistant cells with mutated β-tubulin [see "3.(i).A.(1).3) Effect of eribulin mesilate on drug resistant cell lines"].
- Increased mRNA in βIII-tubulin decreased the antiproliferative effect of taxanes but is suggested to enhance the antiproliferative effect of eribulin mesilate (*Nat Rev Cancer.* 2010;10:194-204. *Lung Cancer*. 2010;67:136-43. *Cancer Chemother Pharmacol.* 2007;60:27-34. *Bull Cancer*. 2005;92:E25-E30).

As explained, the antiproliferative effect of eribulin mesilate on taxane-resistant cells is reduced when resistance is due to overexpressed P-gp, but not when resistance is due to β-tubulin mutations or quantitative changes in βIII-tubulin. Eribulin mesilate is therefore expected to have efficacy in taxane-resistant cells.

PMDA's view on the effects of eribulin mesilate on taxane-resistant cells:
The applicant's explanation is acceptable because the applicant has investigated the mechanism of how eribulin mesilate achieves efficacy on taxane-resistant cells when resistance is due to β-tubulin mutation or quantitative changes in tubulin, and because the mechanism revealed by the applicant has been supported by published literature. However, the mechanism of antiproliferative action of eribulin mesilate on taxane-resistant cells, including that from the molecular perspective, have not been fully clarified for the following reasons. Therefore, the applicant should actively continue to investigate the mechanism and to obtain new knowledge.

- Whether the overexpression of P-gp is involved in the acquisition of resistance to taxanes is unknown.
- Taxane-resistant cells due to overexpressed P-gp are assumed to be resistant not only to taxanes but also to eribulin mesilate [see "3.(i).B.(3) Mechanism of resistance acquisition to eribulin mesilate"].

3.(i).B.(3) Mechanism of resistance acquisition to eribulin mesilate

Knowledge on the mechanism of acquisition of resistance to eribulin mesilate may help determine patient eligibility for the therapy. PMDA asked the applicant to elucidate the mechanism.

The applicant's view:

The possible mechanism of acquisition resistance to eribulin mesilate are as follows: (a) eribulin is metabolically inactivated; (b) the elimination of eribulin from cells is enhanced by drug efflux pumps (e.g., P-gp); and (c) changes occur in tubulin or microtubules. Based on the following facts, overexpressed P-gp is probably involved in the acquisition of resistance to eribulin mesilate:

- In humans, rats, and dogs, eribulin is mostly excreted unchanged. In the nonclinical studies, eribulin-metabolizing enzymes were not induced. Eribulin is therefore hardly metabolized, and metabolic inactivation of eribulin is unlikely to be involved in the acquisition of resistance to the drug [see "3.(ii).A.(3) Metabolism"].
- In the *in vitro* studies, the antiproliferative effect of eribulin mesilate decreased on the multidrug-resistant cell line MES-SA/Dx5-Rx1 overexpressing P-gp [see "3.(i).A.(1).3) Effect of eribulin mesilate on drug resistant cell lines"].
- The antiproliferative effect of eribulin mesilate did not decrease on taxane-resistant cells presenting changes in β-tubulin (mutation and quantitative change) [see "3.(i).A.(1).3) Effect of eribulin mesilate on drug resistant cell lines"].

The applicant intends to conduct an additional study when any new knowledge and data on the mechanism of acquisition of resistance to eribulin mesilate become available from published literature or other sources.

PMDA accepted the applicant's response.

3.(i).B.(4) Peripheral nerve disorder

The applicant's explanation on the onset of peripheral nerve disorder caused by eribulin mesilate:

As compared with other tubulin-targeting agents, eribulin mesilate has a specific mechanism of action with its unique inhibitory effect on microtubule dynamics. Therefore, eribulin mesilate may exert effects different from those of other tubulin-targeting drugs.

Microtubules (tubulins) play an important role not only in cell division but also in transportation in peripheral nerve cells. Peripheral nerve disorders induced by the clinical use of tubulin-targeting drugs are known to be one of dose-limiting toxicities. As compared with PTX, eribulin mesilate caused milder damage on the peripheral nerve [see "3.(i).A.(2).4) Effects on peripheral nervous system"], suggesting that the difference (in the degree of damage on the peripheral nerve) may be attributed to the specific inhibitory effect of eribulin mesilate on microtubule dynamics (i.e., eribulin mesilate inhibits only the

growth phase of microtubules). Therefore, a nonclinical study is currently underway to examine this hypothesis.

PMDA's view on peripheral nerve disorders caused by eribulin mesilate:
The applicant's hypothesis that the peripheral nerve-damaging activity of eribulin mesilate is milder than that of PTX has been examined electrophysiologically and histologically at MTD in mice. However, the credibility of the hypothesis is to be clarified by another nonclinical study being conducted by the applicant to prove the hypothesis, and by knowledge from published literature in the future. Currently available information on peripheral nerve disorders caused by eribulin mesilate should be communicated to healthcare professionals appropriately.

If the applicant attempts to claim that eribulin mesilate causes milder damage on the peripheral nerve than PTX, it should conduct behavioral pharmacology and other relevant studies to collect data showing that the results of the above-mentioned investigation at MTD in mice adequately represent peripheral nerve disorders in humans receiving eribulin mesilate at a clinical dose.

3.(i).B.(5) Safety pharmacology

PMDA asked the applicant the rationale for the feasibility of clinical safety evaluation of eribulin mesilate based on the safety pharmacology study data submitted.

The applicant's explanation:
In the *in vivo* studies, the maximum concentration of eribulin mesilate was 42.2-fold the human C_{max} after administration at a clinical dose. The maximum dose of eribulin mesilate used in the *in vivo* studies was higher than MTD or a dose that would cause obvious toxicity. (The maximum doses were selected based on the results of repeated dose toxicity studies.)

The pharmacokinetics of eribulin were studied in rats to evaluate effects on the central nervous system and the respiratory system. C_{max} was 1.5-fold and $AUC_{0\text{-}inf}$ was 0.2-fold those in Japanese Study E7389-J081-105, indicating that the dose used in the safety pharmacology studies achieved C_{max} greater than that of the clinical dose.

The pharmacokinetics of eribulin were studied in dogs to evaluate effects on the cardiovascular system. $AUC_{0\text{-}inf}$ was 0.2-fold that in Japanese Study E7389-J081-105. As mentioned earlier, the doses used in safety pharmacology studies were lower than the clinical dose. However, the cardiovascular safety of eribulin mesilate in clinical use was evaluated through the monitoring of the cardiovascular system during clinical studies.

PMDA's view on safety pharmacological studies of eribulin mesilate:
Eribulin exposure was lower in the *in vivo* studies evaluating potential cardiovascular risks than in the clinical study. The cardiovascular safety of eribulin mesilate in clinical use thus cannot be fully evaluated

based solely on the safety pharmacology study data. QT/QTc prolongation was reported in Foreign Study E7389-E044-110 [see "4.(ii).A.(7) Foreign phase I study"], despite no change in QT/QTc intervals in the *in vitro* studies. The data from Foreign Study E7389-E044-110 should be provided to healthcare professionals in appropriate manner through written materials [see "4.(ii).B.(5) Effects of eribulin mesilate on QT/QTc intervals"].

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The pharmacokinetic (PK) profiles of eribulin mesilate were evaluated in mice, rats, and dogs. The effects of eribulin mesilate on drug-metabolizing enzymes were evaluated in human biological samples.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose administration

A single dose of eribulin mesilate was administered intravenously at 0.5 or 2 mg/kg to male BALB-c mice to determine the plasma concentration of eribulin (see the table below). The plasma concentration of eribulin decreased rapidly by 1 hour post-dose and slowly thereafter.

PK parameters of single-dose intravenous eribulin mesilate in male BALB-c mice

Dose (mg/kg)	$AUC_{0\text{-last}}$ (ng·h/mL)	MRT_{inf} (h)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
0.5	223	3.05	2.14	6.44	3.55
2	707	4.38	2.79	12.2	6.88

Mean; n = 3/time point.

Following a single dose of eribulin mesilate administered intravenously at 2 mg/kg or orally at 5.5 mg/kg to wild-type or P-gp-deficient CF-1 mice, plasma concentrations were measured to study the involvement of P-gp in the PK of eribulin mesilate (see the table below).

Following the intravenous dose, prolonged $t_{1/2}$ and decreased CL were observed in P-gp-deficient mice as compared with wild-type mice. Because eribulin has been suggested to be excreted in the bile [see "3.(ii).A.(4).2) Biliary excretion"], the applicant explained that these changes were likely to be attributed to decreased biliary excretion resulting from the absence of P-gp.

Following the oral dose, prolonged $t_{1/2}$ and t_{max} and increased $AUC_{0\text{-t}}$ and C_{max} were observed in P-gp-deficient mice as compared with wild-type mice. While bioavailability (BA) was 6.9% in wild-type mice, it was as high as 52.6% in P-gp-deficient mice. The applicant explained that the results suggest the involvement of P-gp in the gastrointestinal absorption of eribulin mesilate.

PK parameters of single-dose intravenous or oral eribulin mesilate in wild-type or P-gp-deficient CF-1 mice

Route	Genotype	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
Intravenous	Wild-type	NA	NA	1048	1.6	4.5	5.9
	P-gp deficient	NA	NA	1722	0.9	8.8	10.2
Oral	Wild-type	1.0	53.2	195	NA	NA	1.9
	P-gp deficient	4.0	264	2401	NA	NA	11.7

Mean; n = 3/time point; NA, not applicable.

A single dose of eribulin mesilate was administered intravenously at 1 or 2 mg/kg to female athymic mice bearing a subcutaneous xenograft of the LOX human malignant melanoma cell line, and the plasma concentration of eribulin was measured (see the table below). The plasma concentration of eribulin decreased rapidly by 1 hour post-dose and slowly thereafter.

PK parameters of single-dose intravenous eribulin mesilate in female athymic mice bearing a subcutaneous xenograft of the LOX cell line

Dose (mg/kg)	AUC_{0-inf} (ng·h/mL)	MRT_{inf} (h)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
1	365	3.3	2.42	8.03	3.7
2	797	3.1	2.22	6.79	5.1

Mean; n = 3/time point.

A single dose of eribulin mesilate was administered intravenously at 1.5 mg/kg or orally at 2.5 mg/kg to male Fischer-344 rats to determine the plasma concentration of eribulin (see the table below). The plasma concentration after the intravenous dose exhibited a triphasic elimination profile. Meanwhile, the plasma concentration after the oral dose was slightly higher than the quantitation limit (5.5 ng/mL) at 0.25 hours post-dose, and PK parameters were not calculated. The absolute BA, however, was assumed to be extremely low based on the time course of the plasma concentration of eribulin. In rats receiving cyclosporine, a P-gp inhibitor, prior to an oral dose of 2.5 mg/kg eribulin mesilate, the plasma concentration of eribulin was higher than that in rats without receiving cyclosporine, and the absolute BA was 18.1%. The applicant provided the following explanation on the increased BA of eribulin in rats receiving cyclosporine: P-gp expressed in small-intestinal epithelial cells was inhibited by cyclosporine, resulting in reduced elimination of eribulin mesilate in the gastrointestinal absorption process.

PK parameters of single-dose intravenous or oral eribulin mesilate in male Fischer-344 rat

Dosing route	Dose (mg/kg)	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-inf} (ng·h/mL)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	BA (%)
Intravenous*1	1.5	NA	4779	826	1.82	18.6	0.03	0.36	11.4	NA
Oral*2,*3	2.5	2.0	58.7	335	NA	NA	NA	NA	9.8	18.1

Mean; *1, n = 6/time point; *2, n = 3/time point; *3, Premedication of cyclosporine; NA, not applicable.

A single dose of eribulin mesilate was administered intravenously at 0.5 or 1 mg/kg to male Sprague-Dawley (SD) rats to determine the plasma concentration of eribulin (see the table below). The applicant explained that the AUC tended to increase with the increase in dose.

PK parameters of single-dose intravenous eribulin mesilate in male SD rats

Dose (mg/kg)	$AUC_{0\text{-inf}}$ (ng·h/mL)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)
0.5	260 ± 69.6	2.04 ± 0.65	36.3 ± 21.0	NA	NA	15.9 ± 7.1
1.0	628 ± 83.9	1.61 ± 0.20	44.1 ± 10.7	NA	NA	27.9 ± 4.1

Mean ± standard deviation (SD); n = 3; NA, not applicable.

In male SD rats given a single oral dose of eribulin mesilate 3 or 10 mg/kg, eribulin mesilate was rapidly absorbed, but the absolute BA was as low as 0.4% (3 mg/kg) and 2.4% (10 mg/kg) as compared with the BA of intravenous 1 mg/kg.

PK parameters of single-dose intravenous or oral eribulin mesilate in male SD rats

Route	Dose (mg/kg)	t_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-inf}}$ (ng·h/mL)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	BA (%)
Intravenous	1	NA	NA	633 ± 12.9	1.39 ± 0.03	38.6 ± 3.9	NA	NA	26.7 ± 2.0	NA
Oral	3	2.0	1.34 ± 0.33	13.2 ± 5.1	NA	NA	NA	NA	7.9 ± 3.5	0.4
	10	2.0	26.0 ± 18.25	171 ± 88.8	NA	NA	NA	NA	21.5 ± 5.4	2.4

Mean ± standard deviation; n = 4; NA, not applicable.

A single dose of ^{14}C-labeled eribulin acetate was administered intravenously at 1 mg/kg to male SD rats to determine the radioactivity levels in blood, plasma, and blood cells. Plasma radioactivity decreased rapidly by 1 hour post-dose and slowly thereafter. The radioactivity levels at 72 hours post-dose decreased to 0.002 μg eq/mL in blood, below the lower limit of quantification in plasma, and 0.001 μg eq/mL in blood cells.

A single dose of eribulin mesilate was administered intravenously at 0.08 mg/kg to male beagle dogs (age, 6-8 months; body weight, 8 kg) to determine the plasma concentration of eribulin (see the table below; Study DSD20[redacted]-42). The plasma concentration of eribulin decreased over time and the $t_{1/2}$ at the terminal phase was 21.9 hours, showing a slow elimination.

PK parameters of single-dose intravenous eribulin mesilate in male beagle dogs (DSD20[redacted]-42)

Age (months)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (ng·h/mL)	$AUC_{0\text{-inf}}$ (ng·h/mL)	MRT_{inf} (h)	CL (L/h/kg)	V_{ss} (L/kg)
6-8	21.9 ± 9.5	64.5 ± 20.1	82.2 ± 27.4	21.5 ± 11.9	1.06 ± 0.36	20.4 ± 5.5

Mean ± standard deviation; n = 4

CL, a PK parameter of eribulin mesilate in Study DSD20[redacted]-42 that are independent of dosage regimen, was 1.06 L/h/kg. The applicant noted a difference between this value and the CL in male beagle dogs (age, 7-14 months; body weight, 9.6-10 kg) receiving intravenous eribulin mesilate at 0.075 mg/kg over 1 hour in a repeated dose toxicity study ([redacted]20B). In order to determine whether the difference was attributable to the different age and body weight of the beagle dogs between the 2 studies, plasma concentrations of eribulin were additionally measured in dogs aged 10-12 months with a body weight similar to that of the dogs in Study [redacted]20B after a single intravenous dose of 0.08 mg/kg (see the table below). The plasma concentrations of eribulin decreased over time. The $t_{1/2}$ at the terminal phase was

28.2 hours, showing a similar elimination trend to that in the dogs aged 6 to 8 months. Given that there was no notable difference in PK between dogs aged 6 to 8 months and those aged 10 to 12 months in Study DSD20[redacted]-42, the applicant explained that the PK of eribulin mesilate was not affected by age (in months) or body weight [Note by the PMDA: Dogs aged 10 to 12 months apparently exhibited prolonged $t_{1/2}$, increased in $AUC_{0\text{-inf}}$, and decreased in CL and V_{ss} as compared with dogs aged 6 to 8 months. How these differences were developed is unknown].

PK parameters of single-dose intravenous eribulin mesilate in male beagle dogs (DSD20[redacted]-42)

Age (months)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (ng·h/mL)	$AUC_{0\text{-inf}}$ (ng·h/mL)	MRT_{inf} (h)	CL (L/h/kg)	V_{ss} (L/kg)
10-12	28.2 ± 4.8	94.7 ± 15.7	118 ± 17.2	28.0 ± 7.0	0.688 ± 0.096	18.8 ± 2.2

Mean ± standard deviation; n = 4

The mean CL in Studies DSD20[redacted]-42 and [redacted]20B was 1.06 L/h/kg (n = 4) and 0.03 L/h/kg (n = 2), respectively. Possible causes of the low CL in Study [redacted]20B are as follows: (a) extrapolated data covering a period from the final time point to infinity contributed greatly to the $AUC_{0\text{-inf}}$ calculated in Study [redacted]20B; and (b) plasma concentrations of eribulin were high in Study [redacted]20B [Note by PMDA: according to the applicant, the causal factors for the high plasma concentrations of eribulin in the study were unknown]. Thus, the applicant presumes that the $AUC_{0\text{-inf}}$ in Study [redacted]20B was estimated to be high, resulting in the low CL.

3.(ii).A.(1).2) Repeated administration

Eribulin mesilate 0.5 or 1 mg/kg was intravenously administered 3 times at 2-day intervals to female athymic mice bearing a subcutaneous xenograft of the LOX cell line, to determine the plasma concentration of eribulin (see the table below). The PK parameters of eribulin after the last dose (Day 5) were similar to those after the administration of a single dose [see "3.(ii).A.(1).1) Single-dose administration"]. Based on the results, the applicant explained that no accumulation of eribulin was observed after repeated doses.

PK parameters of repeated-dose intravenous eribulin mesilate in female athymic mice bearing subcutaneous xenograft of the LOX cell line (Day 5)

Dose (mg/kg)	$t_{1/2}$ (h)	$AUC_{0\text{-inf}}$ (ng·h/mL)	$MRT_{0\text{-inf}}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)
0.5	2.2	161.8	2.8	2.73	7.57
1	2.4	308.6	2.6	2.86	7.41

Mean; n = 3/time point

Eribulin mesilate 0.13 or 0.2 mg/kg was administered over 1 hour as a continuous intravenous infusion 3 times at 4-day intervals to male and female Fischer-344 rats, to determine the plasma concentration of eribulin (see the table below). As a result, 4 of the 9 male rats receiving 0.2 mg/kg died. Therefore, mode of administration of 0.2 mg/kg in female rats was changed from a 1-hour continuous intravenous infusion to a 1-minute intravenous bolus administration, because the former would place a burden on rats. The applicant explained that in male rats, the PK parameters after the first dose (Day 1) and after the last dose (Day 9) were similar, showing no effects of repeated doses on the time course of plasma

concentration of eribulin. Meanwhile, female rats showed increased $AUC_{0\text{-}inf}$ after repeated administration. According to the applicant, this difference is due to a higher incidence of deteriorated systemic condition, decreased body weight, or deaths in female rats than in male rats, and not due to an intrinsic sex difference in PK.

PK parameters following repeated continuous intravenous infusion or intravenous bolus administration of eribulin mesilate to male and female Fischer-344 rats

Dose (mg/kg)	Day of measurement	$t_{1/2}$ (h)		$AUC_{0\text{-}inf}$ (ng·min/mL)		CL (L/h/kg)		V_{ss} (L/kg)	
		Male	Female	Male	Female	Male	Female	Male	Female
0.13	Day 1	4.33	9.00	5108	5414	1.60	1.45	6.279	11.164
	Day 9	5.07	17.23	5429	9261	1.51	0.864	6.311	16.670
0.2	Day 1	NA	8.13	NA	6554	NA	1.82	NA	16.966
	Day 9	4.35	7.25	5235	8912	2.33	1.34	6.000	11.488

Mean; n = 3/time point; NA, not applicable.

Eribulin mesilate 0.004, 0.03, or 0.04 mg/kg was administered over 1 hour as a continuous intravenous infusion 3 times at 4-day intervals to male and female beagle dogs, to determine the plasma concentration of eribulin (see the table below). However, the plasma concentration of eribulin in the 0.004 mg/kg group was too low to determine PK parameters. The accumulation of eribulin was not observed after repeated doses at 0.03 or 0.04 mg/kg. In the 0.03 mg/kg group, the $t_{1/2}$ on Day 1 was higher than that on Day 9. The applicant explained that this difference was due to an error caused by the extrapolation of data covering a period from 24 hours post-dose to infinity, because the $AUC_{0\text{-}inf}$ on Day 1 was higher than that on Day 9, while the $AUC_{0\text{-}24h}$ on Day 1 (48.0 ng·h/mL) was similar to that on Day 9 (53.4 ng·h/mL).

PK parameters following repeated intravenous administration of eribulin mesilate to male and female beagle dogs

Dose (mg/kg)	Day of measurement	$t_{1/2}$ (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	CL (L/h/kg)	V_{ss} (L/kg)
0.03	Day 1	44.98	182	0.214	9.350
	Day 9	15.57	100	0.379	4.709
0.04	Day 1	19.50	115	0.394	6.642
	Day 9	11.07	103	0.395	4.243

Mean; n = 4 (n = 2/sex).

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution

A single dose of eribulin mesilate was administered intravenously at 2 mg/kg or orally at 5.5 mg/kg to wild-type or P-gp-deficient male CF-1 mice, to study the distribution of eribulin to the brain (see the table below). As compared with wild-type mice, P-gp-deficient mice showed delayed t_{max} and higher C_{max} in the brain. After an intravenous dose, the brain penetration index (BPI) in P-gp-deficient mice was higher than that in wild-type mice. The applicant explained that the result suggests the involvement of P-gp in the distribution of eribulin to the brain.

PK parameters following a single intravenous or oral dose of eribulin mesilate in wild-type or P-gp-deficient male CF-1 mice

Route (Dose)	Genotype	$AUC_{0\text{-}t}$ in plasma (ng·h/mL)	$AUC_{0\text{-}t}$ in the brain (ng·h/g)	t_{max} in the brain (h)	C_{max} in the brain (ng/g)	BPI
Intravenous (2 mg/kg)	Wild type	1048	112	0.08	45	0.1
	P-gp deficient	1722	5863	24	352	3.4
Oral (5.5 mg/kg)	Wild type	195	NA	6	5	NA
	P-gp deficient	2401	5125	36	244	2.1

N = 3/time point; NA, not applicable; BPI (brain penetration index) = $AUC_{0\text{-}t\ (brain)}/AUC_{0\text{-}t\ (plasma)}$

A single dose of eribulin mesilate 1 or 2 mg/kg was administered intravenously to female athymic mice bearing a subcutaneous xenograft of the LOX cell line, to study the distribution of eribulin to the brain. The BPI was low in the athymic mice, as in CF-1 mice (see the table below). When eribulin mesilate was administered intravenously 3 times every other day at 0.5 or 1 mg/kg, the concentration of eribulin in the brain was below the quantification limit (4 ng/g) at most time points on Day 5 after the first dose; therefore, BPI could not be calculated. The concentration of eribulin in tumor tissue was higher after repeated doses of 1 mg/kg than after a single dose of 1 mg/kg.

PK parameters following intravenous administration of repeated doses or a single dose of eribulin mesilate to female athymic mice bearing subcutaneous xenograft of the LOX cell line

	Dose (mg/kg)	$AUC_{0\text{-}inf}$ in plasma (ng·h/mL)	$AUC_{0\text{-}inf}$ in the brain (ng·h/g)	$AUC_{0\text{-}inf}$ in tumor tissue (ng·h/g)	BPI	TPI
Single dose	1	365	47.8	6294	0.131	17.2
	2	797	362	18,565	0.454	23.3
Repeated doses (Day 5)	0.5	162	NC	5501	NC	34.0
	1	309	NC	8821	NC	28.6

N = 3/time point; NC, not calculated; BPI (brain penetration index) = $AUC_{0\text{-}inf\ (brain)}/AUC_{0\text{-}inf\ (plasma)}$
TPI (tumor penetration index) = $AUC_{0\text{-}inf\ (tumor)}/AUC_{0\text{-}inf\ (plasma)}$

A single dose of ^{14}C-labeled eribulin acetate 0.75 mg/kg was administered intravenously to male albino SD rats and male pigmented Long-Evans rats to study the tissue distribution of radioactivity by quantitative whole-body autoradiography. In albino rats, the radioactivity level in tissues reached a peak during the 30 minutes post-dose, except in the lymph nodes, testis, seminal vesicle, and esophagus. High radioactivity levels were detected in the lung (12.2 μg eq/g), bladder (7.64 μg eq/g), renal cortex (6.44 μg eq/g), renal medulla (5.41 μg eq/g), liver (4.04 μg eq/g), spleen (2.93 μg eq/g), thyroid (2.54 μg eq/g), stomach (2.37 μg eq/g), and salivary glands (2.29 μg eq/g) as compared with the other tissues (ranged from below the quantification limit [0.012 μg eq/g] to 1.84 μg eq/g). The radioactivity in lymph nodes reached a peak at 0.5 to 6 hours post-dose and then declined over time, as in other tissues. The radioactivity level in most of the tissues examined decreased nearly to the quantification limit during the 7 days post-dose. The radioactivity levels at 5 minutes post-dose in the cerebrum, cerebellum, medulla, and spinal cord were ≤0.028 μg eq/g, which were lower than that in the pituitary gland (1.225 μg eq/g) located outside the blood-brain barrier. According to the applicant, the radioactivity distribution in the central nervous system in this study and those in the brain in P-gp-deficient CF-1 mice suggest that eribulin taken up into cerebral capillary endothelial cells are excreted by P-gp into the blood. The

radioactivity in tissue in pigmented rats was similar to that in albino rats, and did not show a phenomenon of selective radioactivity binding to melanin-containing tissues.

3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells

Plasma protein binding ratios of eribulin (100, 500, or 1000 ng/mL) in mouse, rat, dog, and human plasma samples were examined by the equilibrium dialysis method. The plasma protein binding was 28.5% to 35.9% in mouse plasma, 23.0% to 34.1% in rat plasma, 15.4% to 26.4% in dog plasma, and 48.9% to 65.1% in human plasma, showing interspecific differences. However, the applicant explained that a high degree of plasma protein binding of eribulin was not observed in any of the investigated species.

A single dose of ^{14}C-labeled eribulin mesilate 1.0 mg/kg was administered intravenously to male rats and 0.08 mg/kg to male and female dogs to determine the concentrations of eribulin in plasma and in blood. In rats, the blood-to-plasma ratio of radioactivity 5 minutes to 24 hours post-dose ranged from 0.63 to 1.56. In dogs, the blood-to-plasma ratio of radioactivity 5 to 25 minutes post-dose ranged from 0.94 to 1.18 in males and from 1.04 to 1.25 in females. According to the applicant, these results suggest that eribulin is distributed in blood cells.

3.(ii).A.(2).3) Placental transfer and fetal distribution

No studies were conducted on placental transfer or fetal distribution of eribulin. However, embryo-fetal developmental studies in rats showed increased early resorption, low body weight, total resorption, and teratogenicity including agnathia [see "3.(iii).A.(5) Reproductive and developmental toxicity"], suggesting that eribulin cross the placenta to the fetus. The applicant will include precautionary advice in the package insert that eribulin mesilate should not be administered to pregnant or possibly pregnant women.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro*

In the presence of nicotinamide adenine dinucleotide phosphate (NADPH), eribulin mesilate (1 or 5 μmol/L) was incubated with human liver microsome at 37°C for 30 minutes. The results showed that 12% to 15% of eribulin mesilate was eliminated by metabolism, while no elimination was observed in the S9 fraction or the cytosol.

When eribulin mesilate (1 or 5 μmol/L) was added to microsomes expressing human recombinant CYP3A4, 20% to 39% of eribulin mesilate was metabolized. The metabolism was inhibited by CYP3A4-specific inhibitors, namely 6',7'-dihydroxybergamottin, ketoconazole, and terfenadine, by 85% to 100%, 35% to 63%, and 24% to 54%, respectively. The correlation coefficient between eribulin mesilate metabolic activity in the human liver microsome and testosterone 6β-hydroxylation activity of each testosterone donor was 0.814 at 1 μmol/L of eribulin mesilate and 0.663 at 5 μmol/L, showing a

significant correlation between them. Based on these results, the applicant explained that eribulin mesilate is metabolized mainly by CYP3A4.

Eribulin mesilate (1 or 5 μmol/L) was added to microsomes expressing CYP2C9, CYP2C18, CYP2D6, CYP3A5, CYP19, or UGT2B7. The maximum proportion of eribulin mesilate metabolized by each microsome was 7.1% (CYP2C9), 8.8% (CYP2C18), 9.8% (CYP2D6), 11% (CYP3A5), 12% (CYP19), and 9.4% (UGT2B7).

3.(ii).A.(3).2) ***In vivo***

A single dose of ^{14}C-labeled eribulin acetate was administered intravenously at 0.5, 1, or 1.5 mg/kg to male rats to study metabolites in plasma, urine, bile, and feces. Unchanged eribulin was the major species detected in plasma, urine, bile, and feces, accounting for the following percentages of the total radioactivity: 83.5% to 91.2% in plasma (0.08 to 24 hours post-dose), 95.3% in urine (up to 10 days post-dose), 86.3% in bile (up to 48 hours post-dose), and 75.1% in feces (up to 10 days post-dose). In addition, 3 oxidants, 1 glucose conjugate, 1 metabolite of an unknown structure, and 1 impurity (which is observed in the manufacturing process of the drug substance) were detected, although in smaller amounts than unchanged eribulin. Because the proportion of metabolites of eribulin was low in all samples analyzed, the applicant considers that eribulin mesilate is poorly metabolized.

A single dose of ^{14}C-labeled eribulin acetate was administered intravenously at 0.08 mg/kg to male and female dogs to study metabolites in plasma, urine, and feces. Unchanged eribulin was the major species detected in plasma, urine, and feces, accounting for the following percentages of the total radioactivity: 100% in plasma, 87.6% to 89.6% in urine, and 93.0% to 94.0% in feces. Other components detected were 1 oxidant in plasma, 1 metabolite of an unknown structure in urine, and 1 impurity (which is observed in the manufacturing process of the drug substance) in urine and feces.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Urinary and fecal excretion

Following a single intravenous dose of eribulin mesilate 1.5 mg/kg to male rats, the excretion rates of unchanged eribulin in urine up to 24 hours post-dose were 10.3% to 10.7%.

A single intravenous dose of ^{14}C-labeled eribulin acetate 0.5 mg/kg was administered to male rats to study excretion in urine and feces. Following administration of 0.5 mg/kg, 15.6% of the administered radioactivity was excreted in urine and 64.9% in feces up to 240 hours post-dose.

A single intravenous dose of ^{14}C-labeled eribulin acetate 0.08 mg/kg was administered to male and female dogs. In male dogs, 8.0% of the administered radioactivity was excreted in urine and 84.4% in feces up to 360 hours post-dose. In female dogs, 10.6% of the administered radioactivity was excreted in urine and 86.9% in feces up to 360 hours post-dose.

According to the applicant, these results show that eribulin is excreted mainly unchanged in feces and is partially excreted in urine.

3.(ii).A.(4).2) Biliary excretion

A single intravenous dose of ^{14}C-labeled eribulin acetate 1.5 mg/kg was administered to male bile duct-cannulated rats to study the excretion of radioactivity in bile, urine, and feces. The excretion rates of radioactivity up to 72 hours post-dose were 36.0% in bile, 21.1% in urine, and 2.1% in feces. The applicant explained that the radioactivity in the feces was derived from secretion by the gastrointestinal tract or from urine mixed into the feces.

3.(ii).A.(4).3) Excretion in milk

No studies were conducted on the excretion of eribulin in milk. The milk to plasma concentration ratio of eribulin was estimated by an analysis using a regression equation (*Br J Clin Pharmacol.* 1992;33:501-5) based on an assumption that eribulin is excreted in milk by passive diffusion. The milk to plasma concentration ratio was estimated to be approximately 1.3 to 1.7. According to the applicant, the result indicates that eribulin may be excreted in milk. Therefore, the package insert will note that lactating women should be advised to discontinue breast-feeding during treatment with eribulin mesilate.

3.(ii).A.(5) Pharmacodynamic interactions

3.(ii).A.(5).1) Enzyme inhibition

Eribulin mesilate was added to human liver microsomes in the presence of substrates of CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) for incubation at 37°C for 15 to 60 minutes to study the effect of eribulin mesilate on the CYP450 enzymes. Eribulin mesilate inhibited CYP3A4 (10-hydroxylation activity of *R*-warfarin) in a dose-dependent manner while exhibiting no statistically significant inhibitory effect on the other enzymes.

The inhibitory effect of eribulin mesilate (1 or 5 μmol/L) on CYP3A4 was investigated using human liver microsomes or human recombinant CYP3A4-expressing microsomes. Eribulin mesilate showed an inhibitory activity against CYP3A4-specific *R*-warfarin 10-hydroxylation, testosterone 6β-hydroxylation, and nifedipine dehydration activities. Eribulin mesilate (0-40 μmol/L) and *R*-warfarin (0.4, 1, or 4 mmol/L), testosterone (25, 50, or 100 μmol/L), or nifedipine (10, 40, or 100 μmol/L) were added to the human recombinant CYP3A4-expressing microsomes for incubation at 37°C for 8 to 60 minutes to study the inhibition pattern of eribulin mesilate against CYP3A4. The K_i values of eribulin mesilate against CYP3A4 were 3 to 17 μmol/L. An analysis by the Dixon technique and a nonlinear regression analysis revealed that the inhibition pattern of eribulin mesilate was reversible and competitive.

The effects of eribulin mesilate on the metabolism of drugs that may be used in combination with eribulin mesilate (i.e., midazolam, carbamazepine, diazepam, terfenadine, tamoxifen, and PTX). Eribulin inhibited the metabolism of midazolam, carbamazepine, diazepam, terfenadine, tamoxifen, and PTX in a dose-dependent manner at concentrations ranging from 1 to 10 μmol/L. The maximum inhibition rate was, however, 28.2%, which was lower than that of ketoconazole (≥49.9%), the positive control.

The applicant's explanation:
The K_i values of eribulin against human recombinant CYP3A4 range from 3 to 17 μmol/L. Eribulin at plasma concentrations at the clinical dose (the Japanese phase I study [Japanese Study E7389-J081-105] showed that the unbound C_{max} was 0.36 μmol/L when the protein binding ratio was 50%) is unlikely to inhibit the metabolism of other drugs that are substrates of CYP3A4 [see "4.(ii).A.(6) Foreign phase I study (Foreign Study E7389-E044-109, February 2009 to July 2009)"].

3.(ii).A.(5).2) Enzyme induction

Human hepatocytes were treated with eribulin mesilate (0.05, 0.25, 1, or 5 μmol/L) or a positive control (2,3,7,8-tetrachloro-dibenzo-*p*-dioxin [0.02 or 0.4 μmol/L] or rifampicin [10 or 50 μmol/L]) for 3 days to study CYP1A- and CYP3A-inducing effects of eribulin. Eribulin did not induce either CYP1A (*R*-warfarin 6-hydroxylation activity) or CYP3A (testosterone 6β-hydroxylation activity) at the concentrations examined. Using the same method, CYP2C9- and CYP2C19-inducing effects were also studied in human hepatocytes treated with eribulin mesilate (1, 5, or 10 μmol/L) or a positive control (rifampicin [10-100 μmol/L] or phenobarbital [50-5000 μmol/L]). The results showed no effects of eribulin on tolbutamide 4-methyl hydroxylation activity (CYP2C9) or *S*-mephenytoin 4'-hydroxylation activity (CYP2C19). There were no changes in the protein expression of these CYP enzymes.

Based on the above, the applicant explained that eribulin mesilate is unlikely to induce these CYP enzymes and therefore unlikely to cause drug interactions.

3.(ii).A.(5).3) Transporters

Effects of eribulin mesilate (0, 0.1, 1, 5, or 10 μmol/L) on P-gp-mediated transport activity were investigated using Caco-2 cell monolayer films. Eribulin inhibited the transport of digoxin, a substrate of P-gp, in a dose-dependent manner, but IC_{50} values were estimated to be ≥10 μmol/L. Based on this result, the applicant considers the inhibitory activity on P-gp-mediated transport to be weak. The plasma concentration of free eribulin after administration of the clinical dose is approximately 0.36 μmol/L, which is markedly lower than the estimated IC_{50} value. Eribulin mesilate is therefore unlikely to have any effect on P-gp substrates in clinical use.

In Foreign Study E7389-E044-109, coadministered ketoconazole, a P-gp inhibitor, had no clear effects on the PK of eribulin. According to the applicant, it is unnecessary to disseminate information or issue alert regarding the P-gp-mediated pharmacokinetic interactions of eribulin.

3. (ii).B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA concluded that the applicant's observations on the absorption, distribution, metabolism, excretion, and pharmacokinetic interactions were acceptable.

3.(ii).B.(1) Sex differences in the pharmacokinetics of eribulin in rats

PMDA asked the applicant to explain reasons for sex differences in V_{ss} and $t_{1/2}$ observed in a repeated dose study in rats [see "3.(ii).A.(1).2) Repeated administration"].

The applicant's explanation:

In this study, the PK parameters were calculated using a 2-compartment model. There was no sex difference in the distribution volume of the central compartment, estimated from CL and C_{max}. Meanwhile, because the $t_{1/2\beta}$ in females (9.0 hours) was longer than that in males (4.3 hours) during the β-phase from 1 to 8 hours after the administration of eribulin mesilate at 0.13 mg/kg, the distribution volume of the peripheral compartment in females was higher, resulting in a higher V_{ss} in females as compared with males.

PMDA accepted the applicant's explanation.

3.(ii).B.(2) Transporter-mediated pharmacokinetic interactions

PMDA asked the applicant to explain potential interactions between eribulin and transporters other than P-gp.

The applicant's explanation:

Eribulin mesilate is a basic compound with an amino group at the end of its side chain. It has a relatively large molecular weight of 730 and is unlikely to be a substrate of an organic anion transporter (OAT), organic anion transporting polypeptide (OATP), or multidrug resistance-associated protein 2 (MRP2). Renal clearance of eribulin in Japanese patients with cancer, 220.5 to 454.4 mL/h, is lower than the products (2618-3833 mL/h) of the plasma unbound fractions (range, 0.349-0.511) and the human glomerular filtration rate (7500 mL/h). Eribulin, therefore, is unlikely to be a substrate of an organic cation transporter (OCT) which is involved in tubular secretion. A study on the inhibitory activity of eribulin against a breast cancer resistance protein (BCRP) using a regression equation for the assessment of BCRP inhibitory action (*J Pharmacol Exp Ther.* 2006:317;1114-24) suggests that eribulin is unlikely to inhibit BCRP.

Based on the above, eribulin is unlikely to be a substrate of OAT, OATP, MRP2, or OCT or to inhibit BCRP and, therefore, is unlikely to cause any transporter-mediated drug interaction.

PMDA's view:
No studies have been conducted on the possibility of eribulin being a substrate of a transporter other than P-gp or its induction or inhibitory activities on such transporters. Thus, no concrete data are available on drug interaction between eribulin and transporters other than P-gp. Because eribulin is eliminated by biliary excretion, data should be further collected on the interactions of eribulin with drugs that are substrates of BCRP or MRP2 expressed in the parenchymal hepatocyte membrane on the bile duct side. New findings should be provided to healthcare professionals in an appropriate manner.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

3.(iii).A.(1) Single-dose toxicity

Although no single-dose toxicity studies were conducted, the acute toxicity of eribulin mesilate was investigated based on the results of short-term dose-finding studies in rats and dogs conducted as preliminary studies on repeated toxicity.

In a dose-finding study in rats, 3 intravenous doses of eribulin mesilate were administered at 4-day intervals to male and female Fischer-344 rats at 0, 0.1, 0.25, 0.5, 0.75, 1, 1.5, or 2 mg/kg (equivalent to 0, 0.6, 1.5, 3, 4.5, 6, 9, or 12 mg/m^2, respectively). In the ≥0.5 mg/kg groups, eribulin mesilate was discontinued after the first dose due to deteriorated condition. In the 0.5 mg/kg group, decreased body weight, low blood cell parameters, and changes in parameters indicating decreased nutritional status or liver function were observed, but there was no death. In the ≥0.75 mg/kg groups, decreased body weight and symptoms such as hunchback position, lethargy, and gait abnormality were observed, and most animals were sacrificed moribund on Days 4 to 8. On the basis of these results, the maximum tolerated dose was estimated to be 0.5 mg/kg, and the lethal dose ≥0.75 mg/kg in rats receiving a single intravenous dose.

In a dose-finding study in dogs, 3 intravenous doses of eribulin mesilate were administered at 4-day intervals to male and female beagle dogs at 0, 0.03, or 0.075 mg/kg (equivalent to 0, 0.6, or 1.5 mg/m^2, respectively). In both the 0.03 and 0.075 mg/kg groups, changes in parameters indicating dose-dependent bone marrow depression were observed after the first dose. In the 0.075 mg/kg group, animals were sacrificed after the second dose because of deteriorated condition. Accordingly, a single intravenous dose of 0.075 mg/kg was estimated to be close to the lethal dose in dogs.

3.(iii).A.(2) Repeat-dose toxicity

In a repeated intravenous dose toxicity study in rats, 3 doses of eribulin mesilate were administered to male and female Fischer-344 rats at 4-day intervals at 0, 0.013, 0.13, or 0.2 mg/kg (equivalent to 0, 0.08,

0.8, or 1.2 mg/m^2, respectively) with a 26-day recovery period after the last dose. There were no deaths caused by eribulin mesilate. In the ≥0.13 mg/kg groups, decreased body weight gain or decreased body weight were observed as well as high AST and changes in hematological parameters indicating bone marrow depression. Histological findings included thymic atrophy, decreased cell count in the bone marrow, and testicular epithelial cell degeneration. In the 0.2 mg/kg group, skeletal muscle degeneration was also reported. These changes, other than in the testis, were considered reversible. There were no findings suggesting toxicity of eribulin mesilate at 0.013 mg/kg; therefore, the no observed adverse effect level (NOAEL) for the study was determined to be 0.013 mg/kg.

In a repeated intravenous dose toxicity study in rats, 3 doses of eribulin mesilate were administered to male and female Fischer-344 rats at 7-day intervals at 0, 0.1, 0.2, or 0.25 mg/kg (equivalent to 0, 0.6, 1.2, or 1.5 mg/m^2, respectively) with a 14-day recovery period after the last dose. The $AUC_{0\text{-}24}$ values on Day 15 are presented in the table below. Exposure to eribulin on Day 15 tended to be lower than that on Day 1.

Toxicokinetics in the repeated intravenous dose toxicity study in rats

Dose		0.10 mg/kg	0.20 mg/kg	0.25 mg/kg
Male	$AUC_{0\text{-}24}$, Day 1 (ng·h/mL)*	49.2 ± 7.3	97.0 ± 9.1	143.2 ± 23.0
	$AUC_{0\text{-}24}$, Day 15 (ng·h/mL)	35.1 ± 9.9	59.3 ± 14.2	77.4 ± 4.3
Female	$AUC_{0\text{-}24}$, Day 1 (ng·h/mL)	37.7 ± 6.0	82.2 ± 9.5	100.3 ± 8.3
	$AUC_{0\text{-}24}$, Day 15 (ng·h/mL)	16.5 ± 1.8	49.9 ± 1.5	61.4 ± 5.4

* Mean ± standard deviation (n = 4).

In this study, 2 males in the 0.2 mg/kg group and 1 male in the 0.25 mg/kg group were sacrificed moribund due to deteriorated condition. In all dose groups, changes in hematological parameters suggesting bone marrow depression were observed. Histological findings included decreased cell count in the bone marrow and thymic atrophy. In the ≥0.2 mg/kg groups, high AST and cholesterol levels and low inorganic phosphorus were observed in addition to decreased body weight gain or decreased body weight. Histological findings in the group included decreased testicular epithelial cell count, decreased sperm count or azoospermia in the epididymis, and sciatic nerve degeneration. The changes in the testis and the sciatic nerve did not resolve even after the 14-day recovery period, but the other changes were reversible. Based on these results, the maximum tolerated dose in this study was determined to be 0.1 mg/kg.

In a repeated intravenous dose toxicity study in rats, 3 doses of eribulin mesilate were administered to male and female Fischer-344 rats at 7-day intervals at 0, 0.1, or 0.2 mg/kg (equivalent to 0, 0.6, or 1.2 mg/m^2, respectively) using a batch containing a high level of impurities. There were no deaths in this study. The clinical findings in the study were similar to those in the repeated intravenous dose toxicity study in rats given 3 doses from a batch containing low impurities at 7-day intervals.

A 6-month repeated intravenous dose toxicity study was conducted in male and female Fischer-344 rats. The rats received 3 doses of eribulin mesilate at 7-day intervals at 0, 0.015, 0.05, or 0.15 mg/kg

(equivalent to 0, 0.09, 0.3, or 0.9 mg/m^2, respectively) followed by a 14-day recovery period. This 28-day cycle was repeated 6 times. The $AUC_{0\text{-}t}$ on Day 141 is presented in the table below; the exposure on Day 141 tended to be higher than that on Day 1.

Toxicokinetics in the 6-month repeated intravenous dose toxicity study in rats[*1]

Dose		0.015 mg/kg	0.05 mg/kg	0.15 mg/kg
Male	$AUC_{0\text{-}t}$, Day 1 (ng·h/mL)	NC	5.2-8.2	42.6-64.0
	$AUC_{0\text{-}t}$, Day 141 (ng·h/mL)	4.4-6.2	16.9-19.2	69.1-85.5
Female	$AUC_{0\text{-}t}$, Day 1 (ng·h/mL)	NC	12.3-18.0	35.4-60.7
	$AUC_{0\text{-}t}$, Day 141 (ng·h/mL)	4.7[*2]	18.6-27.7	60.4-89.3[*3]

[*1] The results are shown as range; [*2] n = 1; [*3] n = 3; NC, Data obtained were insufficient for calculating AUC.

There were no deaths attributable to eribulin mesilate. In the ≥0.05 mg groups, decreased red blood cell count, increased reticulocytosis, decreased testicular weight, and high liver and spleen weights were observed. Histological findings were decreased bone marrow cell count and splenic extramedullary hematopoiesis. In the 0.15 mg/kg group, decreased body weight gain (in males only) and high AST, ALT, and cholesterol levels were observed along with histological findings of decreased testicular epithelial cell count and decreased sperm count or azoospermia in the epididymis. The 0.015 mg group showed no findings suggesting the toxicity of eribulin mesilate. Accordingly, the NOAEL in the study was determined to be 0.015 mg/kg.

In a repeated intravenous dose toxicity study in dogs, 3 doses of eribulin mesilate were administered to male and female beagle dogs at 4-day intervals at 0, 0.004, 0.03, or 0.04 mg/kg (equivalent to 0, 0.08, 0.6, or 0.8 mg/m^2, respectively) with a 26-day recovery period following the last dose. The $AUC_{0\text{-}inf}$ on Day 9 was below the quantification limit in both males and females in the 0.004 mg/kg group. In the 0.03 mg/kg group, the $AUC_{0\text{-}inf}$ on Day 9 was 177.0 ng·h/mL in males and 61.1 to 62.8 ng·h/mL in females. In the 0.004 mg/kg group, the $AUC_{0\text{-}inf}$ on Day 9 was 102.7 to 115.6 ng·h/mL in males and 85.4 to 106.6 ng·h/mL in females. These results showed no accumulation after repeated administration. No deaths related to eribulin mesilate occurred in the study. In the ≥0.03 mg/kg groups, decreased white blood cell count was observed. Histological findings were atrophic changes in lymphoid tissues of the spleen and lymph node. In the 0.04 mg/kg group, reticulocytopenia was observed. All of these changes were suggested to be reversible. In the 0.004 mg/kg group, there were no findings suggesting the toxicity of eribulin mesilate. Based on the results, the NOAEL in the study was determined to be 0.004 mg/kg.

In a repeated intravenous dose toxicity study in dogs, 3 doses of eribulin mesilate were administered to male and female beagle dogs at 0, 0.02, 0.04, or 0.05 mg/kg (equivalent to 0, 0.4, 0.8, or 1 mg/m^2, respectively) at 7-day intervals with a 14-day recovery period following the last dose. In males, the $AUC_{0\text{-}24}$ on Day 15 was 8.9, 23.0, and 28.0 ng·h/mL in the 0.02, 0.04, and 0.05 mg/kg groups, respectively. In females, the $AUC_{0\text{-}24}$ on Day 15 was 5.5, 14.5, and 26.6 ng·h/mL in the 0.02, 0.04, and 0.05 mg/kg groups, respectively. These results show no accumulation after repeated administration. The actual doses of eribulin mesilate in this study were lower than the protocol-specified doses by approximately 30% due to absorption to the filter and plastic vial during the preparation of eribulin

mesilate solution. No deaths related to eribulin mesilate occurred in the study. In the ≥0.02 mg/kg groups, high spleen weight and a histological change of splenic extramedullary hematopoiesis were observed. In the ≥0.04 mg/kg groups, decreased white blood cell count was observed. All of these changes were considered reversible, and the maximum tolerated dose in the study was determined to be >0.05 mg/kg.

A 6-month repeated intravenous dose toxicity study was conducted in male and female beagle dogs. The dogs received 3 doses of eribulin mesilate at 7-day intervals at 0, 0.0045, 0.015, or 0.045 mg/kg (equivalent to 0, 0.09, 0.3, or 0.9 mg/m^2, respectively), followed by a 14-day recovery period. This 28-day cycle was repeated 6 times. As shown by the $AUC_{0\text{-}t}$ on Day 141 in the table below, eribulin exposure tended to be higher on Day 141 than on Day 1.

Toxicokinetic results in the 6-month repeated intravenous dose toxicity study in dogs*

Dose		0.0045 mg/kg	0.015 mg/kg	0.045 mg/kg
Male	$AUC_{0\text{-}t}$, Day 1 (ng·h/mL)	0.8-1.2	5.0-6.8	19.7-25.0
	$AUC_{0\text{-}t}$, Day 141 (ng·h/mL)	1.5-9.0	6.3-13.1	27.4-30.7
Female	$AUC_{0\text{-}t}$, Day 1 (ng·h/mL)	1.2-2.3	3.9-6.1	17.1-29.1
	$AUC_{0\text{-}t}$, Day 141 (ng·h/mL)	1.7-2.4	4.5-10.4	16.3-24.1

* The results are shown as range.

No eribulin-associated deaths occurred in the study. The 0.0045 mg/kg group showed no changes related to eribulin mesilate, and the only change seen in the 0.015 mg/kg group was reticulocytopenia. In the 0.045 mg/kg group, decreased white blood cell count, decreased hemoglobin and reticulocyte count, and low testicular weight were observed. Histological findings included increased bone marrow cells (a compensatory change), atrophic changes in lymphoid tissues, decreased testicular epithelial cell count, and decreased sperm count or azoospermia in the epididymis. Accordingly, the NOAEL in the study was determined to be 0.015 mg/kg.

3.(iii).A.(3) Genotoxicity

Genotoxicity studies included a bacterial reverse mutation assay, a mouse lymphoma TK assay, and a rat micronucleus assay. While bacterial reverse mutation was negative, the mouse lymphoma TK assay was weakly positive for both gene mutations and clastogenic effects. Micronucleus was also positive. The bacterial reverse mutation assay and mouse lymphoma TK assay performed on batches with high impurity content yielded similar results to those with low impurity content.

3.(iii).A.(4) Carcinogenicity

No carcinogenicity study was performed because eribulin mesilate is indicated for patients with advanced cancer.

3.(iii).A.(5) Reproductive and developmental toxicity (embryo-fetal developmental toxicity studies)

Eribulin mesilate was administered intravenously at 0, 0.01, 0.03, 0.1, or 0.15 mg/kg (equivalent to 0, 0.06, 0.18, 0.6, or 0.9 mg/m^2, respectively) to pregnant SD rats. A total of 3 doses were given on Gestation Days 8, 10, and 12. In the ≤0.03 mg/kg groups, no effects of eribulin mesilate were observed in maternal animals or in fetuses. In the ≥0.1 mg/kg groups, decreased body weight gain was observed in maternal animals, and increased early resorption and low body weight were observed in fetuses. In the 0.15 mg/kg group, maternal animals showed decreased body weight on the day after treatment and premature labor; 3 maternal animals had total resorption of fetuses; and fetus showed signs suggesting teratogenicity such as agnathia. Accordingly, the NOAEL for maternal animals and fetuses was determined to be 0.03 mg/kg.

3.(iii).A.(6) Local tolerance

No local tolerance studies were performed. However, the findings on injection sites in repeated dose toxicity studies in rats and dogs revealed that eribulin mesilate had no potential to cause local irritation.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Bone marrow toxicity

Bone marrow toxicity of eribulin mesilate on granulo-macrophage colony forming units (CFU-GM) was investigated *in vitro* using mouse, dog, and human bone marrow cells. IC_{90} of eribulin mesilate for colony formation was similar among all animal species examined. Bone marrow toxicity was also investigated on CFC-GEMM. IC_{50} of eribulin mesilate for colony formation was similar between the human and dog samples, but that in the mouse sample was as high as approximately 10-fold that in the human sample, suggesting the low sensitivity in mice. Effects on CFC-GEMM were compared between eribulin mesilate and other drugs in the same class, namely PTX and VLB. Eribulin mesilate, similarly to PTX and VLB, showed dose-dependent activity against CFC-GEMM, suggesting that eribulin mesilate inhibits colony formation.

3.(iii).A.(7).2) Toxicity of impurities

The following impurities are detected in the drug substance or drug product at higher concentrations than the safety qualification thresholds: [redacted], [redacted], [redacted], [redacted], and [redacted]. The safety of these impurities were evaluated based on data from repeated dose toxicity studies and genotoxicity studies submitted and an *in silico* analysis. The results showed that these impurities are very unlikely to cause any safety problems, even when eribulin mesilate is administered at the upper limit of the specified dose for clinical use.

3.(iii).B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA concluded that there is no safety margin for clinical doses of eribulin mesilate. However, because of the seriousness of the target disease, the clinical use of eribulin mesilate is permissible.

The toxicity of eribulin mesilate was observed in tissues with a high cell proliferation activity such as bone marrow, lymphoid, and testis tissues. Eribulin mesilate was also shown to have peripheral neurotoxicity, which is commonly seen with many other tubulin polymerization inhibitors. Hepatotoxicity and teratogenicity of eribulin mesilate were also suggested. Therefore, eribulin mesilate should be administered with due caution in clinical settings.

3.(iii).B.(1) Testicular toxicity

Because of testicular toxicity observed in repeated dose toxicity studies in rats and dogs, PMDA advised the applicant to consider adding precautionary advice in the package insert on the risk of the toxicity in male patients of reproductive potential. The applicant responded that relevant precautionary advice would be included in the package insert.

PMDA accepted the applicant's explanation.

3.(iii).B.(2) Contraception

Due to a risk of teratogenicity, eribulin mesilate is contraindicated in pregnant or possibly pregnant women.

The mechanism of action of eribulin mesilate also suggests its possible effect on early embryonic development. PMDA advised the applicant to consider instructing patients to use contraception during treatment and for a certain period after treatment with eribulin mesilate.

The applicant's response:
The interview form and other written materials will have precautionary advice on the need for contraception during treatment with eribulin mesilate and for 2 months after the last dose.

PMDA accepted the applicant's response.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

Eribulin concentrations in human plasma, urine, feces, and whole blood were measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS).

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The pharmacokinetics of eribulin were studied in patients with cancer who were receiving eribulin mesilate alone or in combination with a CYP3A4 inhibitor.

4.(ii).A.(1) Japanese phase I study (Japanese Study E7389-J081-105, May 2006 to January 2008)

Eribulin mesilate was administered intravenously to 15 patients with advanced solid tumors at 0.7, 1.0, 1.4, or 2.0 mg/m^2 over 2 to 10 minutes on Days 1 and 8 to determine plasma concentrations of eribulin (see the table below). On Days 1 and 8, eribulin at all doses was eliminated from plasma in a triphasic manner within 168 hours after administration.

PK parameters after intravenous administration of eribulin mesilate

	Dose (mg/m^2)	n	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h/m^2)	V_{ss} (L/m^2)	MRT (h)
Day 1	0.7	3	289 ± 43.0	268 ± 101	299 ± 125	36.4 ± 11.2	2.31 ± 0.88	73.7 ± 28.3	32.6 ± 9.1
	1.0	3	381 ± 52.9	319 ± 44.7	380 ± 65.2	42.9 ± 10.9	2.37 ± 0.39	94.4 ± 8.8	40.8 ± 10.4
	1.4	6	519 ± 107	646 ± 106	673 ± 114	39.4 ± 8.3	1.89 ± 0.33	76.3 ± 19.2	40.7 ± 10.1
	2.0	3	718 ± 104	1206 ± 182	1370 ± 282	59.9 ± 13.4	1.32 ± 0.25	86.7 ± 21.8	67.5 ± 22.5
Day 8	0.7	3	313 ± 77.1	302 ± 96.6	336 ± 96.2	37.8 ± 11.3	1.97 ± 0.67	67.7 ± 25.7	34.4 ± 8.3
	1.0	3	453 ± 92.2	366 ± 79.3	418 ± 73.5	36.7 ± 4.3	2.17 ± 0.42	75.9 ± 10.9	35.4 ± 4.7
	1.4	5*	544 ± 52.5	648 ± 131	699 ± 129	38.6 ± 5.2	1.82 ± 0.34	67.8 ± 12.4	37.4 ± 4.8
	2.0	0*	–	–	–	–	–	–	–

Mean ± standard deviation; * On Day 8, 1 subject in the 1.4 mg/m^2 group and al subjects in the 2.0 mg/m^2 group failed to meet the requirements for treatment, and therefore they did not receive eribulin mesilate.

The applicant's discussion on the study results:

The similarities in eribulin PK parameters between Days 1 and 8 demonstrated no accumulation of eribulin. Although there were significant inter-individual differences in C_{max} and AUC_{0-t}, C_{max} generally increased in a dose-proportional manner. At the same time, a more-than-dose-proportional increase was observed in AUC_{0-t} in the 1.4 and 2.0 mg/m^2 groups. In an analysis using a power model ($Y = \alpha X^{\beta}$; X, dose; Y, C_{max} or AUC_{0-t}), the linearity of C_{max} could not be estimated because the point estimate of β was 0.868 with a large 95% confidence interval (95% CI) (0.610, 1.125). The linearity of AUC_{0-t} was not observed because the point estimate of β was 1.527 with 95% CI exceeding 1 (1.162, 1.891). However, it is difficult to make a conclusion on the PK linearity of eribulin only from this single study, because of the small number of subjects (3 to 6) in each dose group used for the linearity analysis.

During 72 hours after administration on Day 1, cumulative urinary excretion rates were 5.01% to 12.88%, and renal clearance ranged from 0.133 to 0.273 L/h/m^2. After the administration of eribulin mesilate at 0.7, 1.0, 1.4, or 2.0 mg/m^2, renal clearance as a percentage of total clearance (1.32 to 2.37 L/h/m^2) was 5.89%, 9.31%, 14.5%, and 20.1%, respectively, showing a trend toward dose-dependent increase. However, given the maximum percentage of 20.1%, the contribution of renal clearance to the elimination of eribulin is not significant.

A relationship of C_{max} and AUC_{0-t} with hematological test values (white blood cell count, neutrophil count, lymphocyte count, red blood cell count, hemoglobin level, and platelet count) on Day 1 was

investigated. The results suggested that the decrease rates of white blood cell count and neutrophil count correlate with the C_{max} and AUC_{0-t} ($R^2 > 0.5$) and, that the decrease rates of white blood cell count and neutrophil count may increase with increased C_{max} and AUC_{0-t}.

4.(ii).A.(2) Foreign phase I study (Foreign Study E7389-A001-101, September 2003 to March 2005)

Eribulin mesilate was administered intravenously to 32 patients with advanced solid tumors over 1 hour at 0.25, 0.5, 0.7, 1.0, or 1.4 mg/m^2 on Days 1, 8, and 15 to determine plasma concentrations of eribulin (see the table below). On Days 1 and 15, eribulin in plasma was eliminated in a biphasic manner at all doses. The PK parameters of eribulin on Day 1 were similar to those on Day 15.

PK parameters after intravenous administration of eribulin mesilate

	Dose (mg/m^2)	n	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h/m^2)	V_{ss} (L/m^2)
Day 1	0.25	2	44	173	32.1	1.93	50.3
	0.5	7*[1]	79 ± 32	338 ± 240	38.0 ± 5.3	1.90 ± 1.14	62.3 ± 36.8
	0.7	4	117 ± 42	512 ± 297	35.8 ± 6.4	1.51 ± 0.74	43.7 ± 15.3
	1.0	9	144 ± 43	653 ± 372	40.5 ± 15.0	1.92 ± 1.34	64.8 ± 30.5
	1.4	9	233 ± 96	856 ± 377	37.2 ± 9.3	1.73 ± 0.78	59.1 ± 26.0
Day 15	0.25	2	106	228	27.6	1.70	41.0
	0.5	6*[2]	80 ± 47	642 ± 835	41.0 ± 14.4	1.98 ± 1.52	67.0 ± 55.6
	0.7	3*[3]	112 ± 40	526 ± 489	27.4 ± 4.7	1.89 ± 1.15	44.3 ± 24.4
	1.0	5*[4]	127*[5] ± 28	412 ± 173	32.7 ± 13.1	2.50 ± 1.1	65.0 ± 20.8
	1.4	4*[2]	247 ± 101	913 ± 694	35.6 ± 18.5	1.88 ± 0.98	47.3 ± 8.0

Mean ± standard deviation

*[1] Plasma eribulin concentration could not be measured in 1 subject because of thawing of the relevant frozen plasma sample.

*[2] Two subjects in the 0.5 mg/m^2 group and 5 subjects in the 1.4 mg/m^2 group did not receive treatment on Day 15, when they failed to meet the requirements for treatment.

*[3] Blood was not drawn from 1 subject.

*[4] Three subjects did not receive treatment on Day 15 because, on Day 5, they failed to meet the requirements for the next treatment. Blood collection was performed no later than 1.5 hours after administration.

*[5] n = 6

During 72 hours after administration on Day 1, cumulative urinary excretion rates were 4.3% to 7.9% and renal clearance ranged from 0.059 to 0.157 L/h/m^2.

A relationship of the incidence of neutropenia, a dose limiting toxicity (DLT) in this study, with C_{max} and $AUC_{0-\infty}$ of eribulin was investigated by a pharmacokinetic/pharmacodynamic (PK/PD) analysis using neutrophil count as a continuous variable. For PK/PD models, an E_{max} model was used for C_{max} (the E_{max} model was selected as the final model because the data fit a sigmoid E_{max} model with a Hill factor of 1) and a sigmoid E_{max} model was used for the $AUC_{0-\infty}$. In this analysis, the exposure corresponding to a 50% decrease in neutrophil count was 187 ng/mL for C_{max} and 824 ng·h/mL for the $AUC_{0-\infty}$.

4.(ii).A.(3) Foreign phase I study (Foreign Study E7389-A001-102, August 2003 to April 2005)

Eribulin mesilate was administered intravenously to 21 patients with advanced solid tumors over 1 hour at 0.25, 0.5, 1.0, 2.0, 2.8, or 4.0 mg/m^2 on Day 1 to determine plasma concentrations of eribulin (see the

table below). The plasma concentration of eribulin exhibited the same elimination behavior as in Foreign Study E7389-A001-101. Although the limited number of patients in each treatment group precluded any conclusion, the applicant explained that C_{max} and $AUC_{0-\infty}$ of eribulin showed a nearly linear increase with increasing doses ranging from 0.25 to 4.0 mg/m^2 (0.221 to 3.536 mg/m^2 as free base).

PK parameters after intravenous administration of eribulin mesilate (Day 1 of cycle 1)

Dose (mg/m^2)	n	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h/m^2)	V_{ss} (L/m^2)
0.25	1	44	138	35.2	1.60	53.3
0.5	4	63 ± 18	210 ± 55	34.4 ± 6.9	2.22 ± 0.58	67.6 ± 25.0
1.0	3	127 ± 39	486 ± 330	45.9 ± 22.0	2.42 ± 1.38	86.7 ± 11.3
2.0	7	369 ± 37	1842 ± 847	48.8 ± 22.0	1.16 ± 0.55	47.8 ± 10.0
2.8	3	340 ± 133	1412 ± 621	42.3 ± 6.8	2.12 ± 1.25	87.4 ± 48.9
4.0	3	528 ± 180	2334 ± 910	66.0 ± 21.8	1.70 ± 0.75	114.2 ± 16.0

Mean ± standard deviation

During 72 hours after administration, cumulative urinary excretion rates were 5.9% to 12.3%, and renal clearance ranged from 0.093 to 0.327 L/h/m^2.

A relationship between eribulin exposure (C_{max} and the $AUC_{0-\infty}$) and the incidence of neutropenia was investigated by a PK/PD analysis using a sigmoid E_{max} model for each PK parameter. The results showed that the exposure corresponding to a 50% decrease in neutrophil count was 117 ng/mL for C_{max} and 396 ng·h/mL for the $AUC_{0-\infty}$.

4.(ii).A.(4) Foreign phase I study (Foreign Study E7389-E044-103, March 2009 to June 2009)

A total of 6 patients with advanced solid tumors received 2 mg of ^{14}C-labeled eribulin mesilate on Day 1 and 1.4 mg/m^2 of unlabeled eribulin mesilate on Day 8. Both were administered as a single intravenous dose over 2 to 5 minutes to investigate the mass balance of eribulin. As shown in the table below, the time courses of plasma concentrations of radioactivity and eribulin were similar. According to the applicant, this result suggests that unchanged eribulin was the predominant species in plasma. The blood-to-plasma ratio of eribulin and radioactivity were calculated to be 0.33 to 1.29 and 0.46 to 1.1, respectively, based on the plasma and blood concentrations of eribulin and radioactivity. This suggests that ^{14}C-labeled eribulin-related radioactivity is distributed mainly into plasma.

The mean excretion rate of radioactivity up to 168 hours after administration was 77.6% (unchanged, 61.3%) in feces and 8.9% (unchanged, 8.1%) in urine, indicating that most radioactivity was eliminated unchanged. According to the applicant, eribulin is eliminated primarily in feces unchanged.

PK parameters of ^{14}C-labeled eribulin after intravenous administration

	C_{max} (ng eq/mL or ng/mL)	AUC_{0-t} (ng eq·h/mL or ng·h/mL)	$AUC_{0-\infty}$ (ng eq·h/mL or ng·h/mL)	$t_{1/2}$ (h)	CL (L/h/m^2)	CL_R (L/h/m^2)	V_{ss} (L/m^2)
Radioactivity	449 ± 137	568 ± 392	753 ± 403*	42.3 ± 17.2*	–	–	–
Eribulin	444 ± 144	627 ± 386	681 ± 425	45.6 ± 8.7	1.82 ± 0.60	0.14 ± 0.04	68.6 ± 14.3

Mean ± standard deviation; n = 6; * n = 5

4.(ii).A.(5) Foreign phase I study (Foreign Study E7389-E044-108, February 2008 to March 2009)

Eribulin mesilate was administered intravenously to 17 patients with solid tumors who had hepatic impairment over 2 to 5 minutes on Days 1 and 8, to study the influence of hepatic impairment on the pharmacokinetics of eribulin. The subjects were classified into 3 groups: normal hepatic function, mild hepatic impairment (Child-Pugh A), and moderate hepatic impairment (Child-Pugh B). Subjects with normal hepatic function received eribulin mesilate 1.4 mg/m^2, those with mild hepatic impairment 1.1 mg/m^2, and those with moderate hepatic impairment 0.7 mg/m^2. The CL of eribulin was lower in subjects with mild or moderate hepatic impairment (0.96-1.55 L/h/m^2) than in subjects with normal hepatic function (2.33 L/h/m^2). The $t_{1/2}$ was longer in subjects with mild or moderate hepatic impairment (41.1-65.4 hours) than in subjects with normal hepatic function (36.1 hours). The dose-normalized geometric mean ratios for C_{max} were 114.7% [90% CI, 82.7%, 159.2%] (mild impairment/normal) and 148.1% [90% CI, 101.3%, 216.6%] (moderate impairment/normal). The dose-normalized geometric mean ratios for $AUC_{0-\infty}$ were 174.8% [90% CI, 115.5%, 264.5%] (mild impairment/normal) and 278.6% [90% CI, 172.3%, 450.6%] (moderate impairment/normal). These results suggested that eribulin exposure increases in patients with hepatic impairment.

4.(ii).A.(6) Foreign phase I study (Foreign Study E7389-E044-109, February 2009 to July 2009)

A crossover study was conducted in 12 patients with advanced solid tumors to investigate the influence of ketoconazole on the pharmacokinetics of eribulin. The subjects received a single intravenous dose of eribulin mesilate 1.4 mg/m^2 alone and eribulin mesilate 0.7 mg/m^2 in combination with ketoconazole, a CYP3A4 inhibitor (see the table below). The dose-normalized C_{max} and $AUC_{0-\infty}$ of eribulin were similar with or without concomitant ketoconazole (see the table below). The applicant therefore explained that no precautionary statements are needed in terms of coadministration of eribulin mesilate and ketoconazole.

PK parameters after intravenous administration of eribulin mesilate

	Eribulin dose (mg/m^2)	n*[1]	C_{max} (ng/mL)	Dose-normalized C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	Dose-normalized $AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (L/h/m^2)	V_{ss} (L/m^2)
Eribulin alone	1.4	10	207 ± 73.9	86.4 ± 33.3	971 ± 372*[2]	406 ± 159*[2]	45.6 ± 13.6*[2]	1.55 ± 0.87*[2]	77.0 ± 29.7*[2]
Eribulin + ketoconazole	0.7	10	106 ± 33.7	89.2 ± 31.9	482 ± 242*[3]	410 ± 205*[3]	40.5 ± 7.69*[3]	1.67 ± 1.05*[3]	70.2 ± 34.7*[3]

Mean ± standard deviation

*[1] Two subjects were excluded from the analysis population (one was withdrawn from eribulin therapy because of an adverse event, and the other was withdrawn from the study because of deviation from the protocol-specified administration method).

*[2] n = 9; *[3] n = 7; Dose-normalized C_{max} and $AUC_{0-\infty}$, relevant parameter values normalized to 1 mg of eribulin mesilate

4.(ii).A.(7) Foreign phase I study (Foreign Study E7389-E044-110, February 2009 to July 2009)

Eribulin mesilate was administered intravenously to 26 patients with advanced solid tumors at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 to study the influence of eribulin on ECG data. The maximum change from baseline in the mean QTcF on Day 1 was 2 milliseconds (95% CI upper limit, 6.7

milliseconds), showing practically no difference between baseline and Day 1. Meanwhile, the maximum change from baseline in the mean QTcF on Day 8 was 11 milliseconds (95% CI upper limit, 19.5 milliseconds), which was longer than that on Day 1.

The applicant's discussion on the influence of eribulin on QTc intervals:
The change from baseline in individually heart rate-corrected QT interval (QTcNi) was similar to that of QTcF, indicating that the prolonged QTcF observed in the study was not attributed to overcorrection of heart rates. However, an analysis using a linear mixed effects model showed no obvious correlation between plasma eribulin concentrations and changes in QTcF, the prolonged QTcF observed after the administration of eribulin mesilate may have been associated with factors such as electrolyte disturbances, other adverse events, and concomitant medications. Stratified analyses showed that the change from baseline in QTcF on Day 8 ranged from 9 to 18 milliseconds in female subjects and –2 to 7 milliseconds in male subjects. QTcF tended to be more prolonged in female subjects than in male subjects. However, the analysis covered only 13 male subjects and 13 female subjects, and this precluded any definite conclusion about sex differences.

4.(ii).A.(8) Population pharmacokinetic (PPK) analysis

A population pharmacokinetic (PPK) analysis using a nonlinear mixed effect model (NONMEM) was conducted on plasma eribulin concentrations (n = 269; 2729 observations) obtained from a Japanese phase I study (Japanese Study E7389-J081-105) and 7 foreign phase I and II studies (Foreign Studies E7389-A001-101, E7389-A001-102, E7389-E044-103, E7389-E044-108, E7389-E044-109, E7389-E044-110, and E7389-G000-211). Plasma eribulin concentrations were fitted to a 3-compartment model, and the following covariates on eribulin clearance (CL) were evaluated: weight, albumin level, total bilirubin level, alkaline phosphatase (ALP) level, coadministration of CYP3A4 inhibitors or inducers, race, age, sex, and creatinine clearance (Ccr). According to calculations, CL increased from 1.66 to 4.38 L/h when weight increased from 40.9 to 146 kg, and CL also increased from 0.91 to 2.0 L/h as albumin level increased from 1.50 to 4.50 g/dL. On the other hand, CL tended to decrease from 4.56 to 2.06 L/h when the total bilirubin level increased from 0.1 to 5 g/dL, and CL also tended to decrease from 2.99 to 1.73 L/h when ALP increased from 27 to 1265 IU/L. Weight was found to be a covariate on the distribution volume of the central compartment, which tended to increase from 273 to 752 L when weight increased from 40 to 110 kg. The applicant reported that the pharmacokinetics of eribulin were not affected by age, sex, race, coadministration of CYP3A4 inhibitors or inducers, or Ccr.

4.(ii).A.(9) Population pharmacokinetic/pharmacodynamic (PPK/PD) analysis

4.(ii).A.(9).1) Relationship between pharmacokinetics and adverse events of eribulin mesilate

Using plasma eribulin concentrations obtained from 209 subjects (774 observations) in Foreign Study E7389-G000-211, an exploratory analysis was performed to examine relationships between "doses, C_{max} or AUC" and "the incidences of the adverse events reported at the highest grades in each treatment cycle (i.e., Grade 3 fatigue, peripheral nerve disorder, and Grade 4 neutropenia)."

No relationship was found between the incidence of fatigue and eribulin exposure.

The incidence of peripheral nerve disorder slightly increased with increasing eribulin exposure. Plots of the incidence, AUC, and the number of treatment cycles undergone showed that the incidence of peripheral nerve disorder increased up to approximately 10% with increasing number of treatment cycles. A logistic regression analysis predicted that when the number of treatment cycles increases from 2 to 10, the incidence of Grade 3 peripheral nerve disorder increases from 0.44% to 0.63% in a patient with an AUC of 500 μg·h/L and from 0.63% to 1.34% in a patient with an AUC of 2500 μg·h/L. However, in Foreign Study E7389-G000-211, the AUC after administration at the proposed clinical dose (1.4 mg/m^2) ranged from 709 to 851 μg·h/L; in this range of AUC, the predicted incidence of Grade 3 peripheral nerve disorder is as low as approximately 1%. Based on the above, the applicant explained that an increase in the incidence of peripheral nerve disorder with increasing number of treatment cycles is not clinically significant [Note by PMDA: In Foreign Study E7389-G000-211, the incidences of peripheral nerve disorder in Cycles 4, 5, 8, and 10 were 4.1%, 3.4%, 6.4%, and 3.6%, respectively].

The incidence of Grade 4 neutropenia increased up to approximately 30% with increasing AUC. Plots of the grade of neutropenia, AUC, and liver function values (i.e., ALT, AST, and total bilirubin) showed that the incidence of Grade 4 neutropenia increased with increasing liver function values. A logistic regression analysis was performed on the relationships among the incidence of Grade 4 neutropenia, AUC, and liver function values. The analysis predicted that when AUC increases from 500 to 2500 μg·h/L, the incidence of Grade 4 neutropenia increases from 4% to 13% in a patient with AST of 40 IU/L and from 7% to 25% in a patient with AST of 100 IU/L. Therefore, the incidence of Grade 4 neutropenia in patients with hepatic impairment is likely to be higher than in those with normal hepatic function.

4.(ii).A.(9).2) Pharmacokinetics and the incidence of neutropenia in patients with hepatic impairment

Using subject characteristics data from Foreign Study E7389-E044-108 in patients with solid tumors and hepatic impairment, changes in plasma eribulin concentration were simulated based on the final model with covariates detected in "4.(ii).A.(8) Population pharmacokinetic (PPK) analysis." The doses used in the simulation were 1.4 mg/m^2 in patients with normal hepatic function and 0.7 or 1.4 mg/m^2 in patients with moderate hepatic impairment. As a result, AUC in patients with moderate hepatic impairment receiving 0.7 mg/m^2 (1141 ng·h/L) was comparable to that in patients with normal hepatic function receiving 1.4 mg/m^2 (1053 ng·h/L). AST is higher in patients with moderate hepatic impairment than in those with normal hepatic function; this suggests that the incidence of Grade 4 neutropenia following administration of 0.7 mg/m^2 is higher in patients with moderate hepatic impairment than in patients with normal hepatic function.

4.(ii).A.(9).3) Relationship between the pharmacokinetics and efficacy of eribulin mesilate

Using the AUC calculated from plasma eribulin concentrations obtained from 209 subjects (774 observations) and efficacy data (indices: response rate, progression free survival [PFS], and overall survival [OS]) from Foreign Study E7389-G000-211, efficacy parameters were plotted by AUC quartile (ranges, <499.2; 499.2-712.4; 712.4-980.05; and >980.05) to explore the relationship between the AUC and efficacy. No relationships were observed between the eribulin AUC and response rate, PFS, or OS.

4.(ii).A.(10) Discussions of the pharmacokinetics of eribulin in Japanese and non-Japanese patients

In Japanese Study E7389-J081-105 and Foreign Studies E7389-A001-101, E7389-A001-102, and E7389-E044-103, the mean range of CL, $t_{1/2}$, V_{ss} and urinary excretion rate were compared between Japanese and non-Japanese subjects, because these PK parameters are independent of dosing methods (dose, dosing time, or dosing schedule). The results were as follows: CL, 1.32 to 2.37 L/h/m^2 (Japanese) and 1.16 to 2.42 L/h/m^2 (non-Japanese); $t_{1/2}$, 36.4 to 59.9 hours (Japanese) and 32.1 to 66.0 hours (non-Japanese); V_{ss}, 73.7 to 94.4 L/m^2 (Japanese) and 43.7 to 114.2 L/m^2 (non-Japanese); urinary excretion rate, 5.01% to 12.88% (Japanese) and 4.29% to 12.31% (non-Japanese). Accordingly, the applicant considers that there is no ethnic difference between Japanese and non-Japanese patients in the pharmacokinetics of eribulin.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Pharmacokinetic linearity of eribulin

The applicant explained that definite conclusions on the pharmacokinetic linearity of eribulin cannot be drawn based solely on the results of the Japanese phase I study (Japanese Study E7389-J081-105) because of its limited sample size [see "4.(ii).A.(1) Japanese phase I study"].

PMDA asked the applicant to explain the PK linearity of eribulin based also on the results of foreign clinical studies.

The applicant's response:

In Foreign Studies E7389-A001-101 and E7389-A001-102 and Japanese Study E7389-J081-105, at the doses ranging from 0.25 to 4 mg/m^2, PK parameters, namely, CL, $t_{1/2}$, and V_{ss}, showed significant interindividual variability but were distributed around fixed values irrespective of dose levels. These results indicate overall linearity in the pharmacokinetics of eribulin.

PMDA asked the applicant to explain the reason why $AUC_{0\text{-}t}$ increased more than dose-proportionally in the 1.4 and 2.0 mg/m^2 groups of Japanese Study E7389-J081-105.

The applicant's explanation:

Patients receiving 1.4 and 2.0 mg/m^2 showed more than dose-proportional increases in AUC_{0-t} because they had lower CL than those receiving other doses. The PPK analysis suggested that CL of eribulin decreases with increasing total bilirubin or ALP. In patients receiving 1.4 or 2.0 mg/m^2, the total bilirubin ranged from 0.6 to 0.8 mg/dL and ALP from 390 to 409 IU/L. These values were higher than those in patients receiving other doses (total bilirubin, 0.4 to 0.5 mg/dL; ALP, 233 to 325 IU/L). According to the PPK analysis, CL is estimated to decrease by approximately 15% to 40% in the total bilirubin (0.6 to 0.8 mg/dL) and ALP ranges (390 to 409 IU/L). This estimate is generally consistent with the decreases in CL observed in this study. Therefore, the more than dose-proportional increases in AUC is probably attributable to decreased CL. Meanwhile, weight was also included in the PPK analysis as a covariate, but the weight of patients in the 1.4 and 2.0 mg/m^2 groups was not low enough to account for the decreased CL as compared with those in the other groups. Weight is therefore considered a minor influential factor.

The effects of intrinsic clearance on changes in CL was examined, and the following results were yielded.

A patient weighing 70 kg has a body surface area of 1.85 m^2 and a hepatic blood flow of 1150 mL/min (37.3 L/h/m^2 after unit conversion [*Pharm Res.* 1993;10:1093-5]). The CL-to-hepatic blood flow ratios of eribulin ranged from 0.035 to 0.064 at the doses studied. Given these facts, the PK of eribulin is limited by intrinsic clearance. Intrinsic clearance may be affected by the expression and activity levels of drug-metabolizing enzymes and transporters. Eribulin is a P-gp substrate and is excreted mainly in feces. The elimination of eribulin is therefore assumed to depend largely on P-gp-mediated biliary excretion. In other words, in patients with impaired hepatic function, decreased P-gp expression and activity would have caused a decline in intrinsic clearance, fluctuating CL.

Based on the above discussions, the more than dose-proportional increases in the AUC_{0-t} of eribulin in patients receiving 1.4 and 2.0 mg/m^2 were attributable to decreased biliary excretion of eribulin resulting from fluctuating P-gp expression or activity level due to impaired hepatic function.

PMDA's view:
The PPK analysis results suggest that lower CL in patients receiving 1.4 or 2.0 mg/m^2 may be due to their lower hepatic function as compared with patients receiving other doses. However, much remains unknown about a relationship between hepatic function changes and the expression or activity levels of P-gp; therefore there is scant evidence to support the idea that the decreased CL in the 1.4 and 2.0 mg/m^2 groups was due to decreased hepatic function. In addition, the mechanism of decreased CL in question has not been elucidated, and a foreign study (Foreign Study E7389-A001-102) showed a decreasing trend in CL with 2.0 mg/m^2 eribulin mesilate as in Japanese Study E7389-J081-105. This finding does not preclude the possibility that the pharmacokinetics of eribulin at ≥1.4 mg/m^2 doses may indicate nonlinearity.

4.(ii).B.(2) Pharmacokinetics in Japanese and non-Japanese patients

Based on the results of Japanese and foreign studies, the applicant discussed that there is no ethnic difference in the pharmacokinetics of eribulin between Japanese and non-Japanese patients [see "4.(ii).A.(10) Discussions of the pharmacokinetics of eribulin in Japanese and non-Japanese patients"].

PMDA's view:

A detailed analysis of ethnic differences in the pharmacokinetics of eribulin between Japanese and non-Japanese patients has a limitation because of the small number of Japanese patients involved in the submitted study results and significant interindividual differences shown in the PK parameters of eribulin. However, the submitted study data show no obvious difference in the pharmacokinetics of eribulin between Japanese and non-Japanese patients.

4.(ii).B.(3) Duration of intravenous infusion

The proposed duration of intravenous infusion is 2 to 5 minutes in accordance with the specifications in Japanese Study E7389-J081-221 and a foreign phase III study conducted as a confirmatory study (Foreign Study E7389-G000-305). However, in the earlier stages of development, infusion time varied by study: 1 hour in Foreign Studies E7389-A001-101 and E7389-A001-102, 1 to 2 minutes in Foreign Study NCI-5730, and 2 to 10 minutes in Japanese Study E7389-J081-105.

PMDA asked the applicant to explain, from a clinical pharmacological perspective, the rationales for the proposed infusion time (2 to 5 minutes) and the reasons the infusion time (2 to 5 minutes) was used in Japanese Study E7389-J081-221 and Foreign Study E7389-G000-305.

The applicant's response:

In both Foreign Studies E7389-A001-101 (1 cycle consisting of 3-week treatment followed by a 1-week recovery period) and E7389-A001-102 (1 cycle consisting of 1-week of treatment followed by a 2week recovery period), the infusion time was 1 hour. In Foreign Study E7389-A001-101, however, the dose intensity (total dose received in each cycle/week) at the MTD (1.0 mg/m^2) was 0.75 mg/m^2/week, which was higher than that (0.67 mg/m^2/week) at the MTD (2.0 mg/m^2) in Foreign Study E7389-A001-102. The dose intensity in Foreign Study E7389-A001-101 was also compared with that in Foreign Study NCI-5730. Both studies employed the same dosing schedule but different duration of intravenous infusion (E7389-A001-101, 1 hour; NCI-5730, 1-2 minutes). Study NCI-5730 showed a higher dose intensity (1.05 mg/m^2/week at the MTD of 1.4 mg/m^2) than Study E7389-A001-101. The results of these studies demonstrated increased per-cycle dose intensity with shorter duration of intravenous infusion. Therefore, in subsequent Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305, time of intravenous infusion was reduced to 2 to 5 minutes for clinical convenience. In the protocol of Japanese Study E7389-J081-105, the infusion time range was defined as 2 to 10 minutes because of safety concerns. However, eribulin mesilate was actually administered over 5 to 6 minutes to all the

subjects in the study. Consequently, the 2 to 5 minute-infusion time was used in the subsequent Japanese Study E7389-J081-221, as in foreign phase II and III studies.

PMDA's view:
According to the applicant, the proposed duration of intravenous infusion was determined based on dose intensity and clinical convenience. However, since Foreign Studies E7389-A001-101 and NCI-5730 had different MTDs despite the same dosing schedule, the comparison between these studies may not provide evidence for a correlation between shorter dosing duration and higher dose intensity. The determination of a safe and effective dosing regimen is described in "4.(iii).B.(5).1) Dosage and administration."

4.(ii).B.(4) Use in patients with hepatic impairment

Foreign Study E7389-E044-108 in patients with solid tumors who had hepatic impairment showed that impaired hepatic function led to increased AUC and prolonged $t_{1/2}$ of eribulin. Foreign Study E7389-G000-211 suggested that the incidence of Grade 4 neutropenia increases with increasing AUC of eribulin.

Because eribulin mesilate is expected to be used in patients with hepatic impairment in clinical settings, PMDA asked the applicant's view on the need of precautionary advice and dose adjustment for this patient population.

The applicant's response:
Patients with hepatic impairment were excluded from Japanese and foreign clinical studies if they had either (1) total bilirubin above the upper limit of normal of historical data at the site; or (2) AST or ALT higher than 2.5-fold the upper limit of normal of historical data at the site. In these patients, eribulin mesilate may increase the incidence of Grade 4 neutropenia. In Foreign Study E7389-E044-108, marked changes in PK parameters, including increases in the AUC and $t_{1/2}$, were reported in patients with hepatic impairment, and therefore precautionary advice and dose adjustment are necessary for this patient population. Advice to the effect that "dose reduction should be considered for patients with hepatic impairment classified into any Child-Pugh class" is to be added in the "Precautions for Dosage and Administration" section of the package insert.

PMDA accepted the applicant's response and reached the following conclusions:
The dose of eribulin mesilate should be adjusted in patients with hepatic impairment for the following reasons:
(a) Foreign Study E7389-E044-108 revealed increased AUC in patients with hepatic impairment.
(b) The results of a PPK/PD analysis suggested that the incidence of Grade 4 neutropenia increases with increasing AUC.

However, because of lack of information on the efficacy or safety of eribulin mesilate at a reduced dose in this patient population, there are no plausible grounds to establish specific dose adjustment rules. In patients with hepatic impairment, therefore, the dose of eribulin mesilate should be reduced as needed in light of the data from Foreign Study E7389-E044-108, and the patients should be carefully and frequently followed during treatment. The results of Foreign Study E7389-E044-108 in patients with hepatic impairment should be adequately communicated to healthcare professionals via the package insert, etc.

4.(ii).B.(5) Effect of eribulin mesilate on the QT/QTc intervals

Prolonged QTcF was reported in some subjects on Day 8 in Foreign Study E7389-E044-110. The event may have been attributed to eribulin. In the entire study population, however, there was no clear correlation between plasma eribulin concentrations and changes in QTcF. Prolonged QTcF, therefore, may have been due to electrolyte disturbances, other adverse events, or concomitant medications [see "4.(ii).A.(7) Foreign phase I study"].

PMDA asked the applicant whether any relationship was observed between prolonged QTcF and the above-mentioned factors other than eribulin (i.e., electrolyte disturbances, other adverse events, concomitant medications) based on the results of Foreign Study E7389-E044-110. The applicant responded that there was no clear relationship between them.

PMDA considers that precautionary advice on QTcF prolongation is unnecessary, because Foreign Study E7389-E044-110 failed to show a relationship between plasma eribulin concentrations and QTcF prolongation, and because nonclinical safety pharmacology studies showed no effects of eribulin on the QT/QTc interval [see "3.(i).A.(2) Safety pharmacology"]. However, because of unknown cause of QTcF prolongation in Foreign Study E7389-E044-110, data from the study should be provided to healthcare professionals in an appropriate manner using suitable materials [see "3.(i).B.(5) Safety pharmacology"].

4.(ii).B.(6) Ongoing clinical pharmacology studies

The applicant's explanation on the ongoing foreign clinical study in patients with cancer and renal impairment (Study [redacted]).

Eribulin mesilate is administered intravenously at 0.7, 1.1, or 1.4 mg/m^2 to patients with normal renal function (Ccr, >60 mL/min), moderate renal impairment (Ccr, 40-59 mL/min), or severe renal impairment (Ccr, 20-40 mL/min) (target total sample size, 77) to investigate the pharmacokinetics, safety, and efficacy of eribulin mesilate. Because this is a [redacted]-initiated study, the target completion date of the final report is unknown.

Besides Study [redacted], a study on drug interactions between eribulin and a CYP3A4 inducer (rifampicin) or an anticancer drugs ([redacted] [redacted], [redacted], [redacted], [redacted], [redacted], or [redacted]) is underway outside Japan.

PMDA's view:
If impaired renal function is found to cause any pharmacokinetic change in eribulin in Study [redacted], the applicant should consider issuing an alert on the matter. The results of Study [redacted], including the ongoing study on drug interaction, should be communicated to healthcare professionals in a prompt and appropriate manner.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The results from 11 studies were submitted: 1 Japanese phase I study, 1 Japanese phase II study, 6 foreign phase I studies, 2 foreign phase II studies, and 1 foreign phase III study. The results from 3 foreign clinical studies were also submitted as reference data.

List of clinical studies

Data type	Study region	Study identifier	Phase	Target patients	n	Dosage regimen	Main endpoints
Evaluation data	Japan	E7389-J081-105	I	Patients with advanced solid tumors	15	Eribulin mesilate was administered intravenously at 0.7, 1.0, 1.4, or 2.0 mg/m^2 over 2 to 10 minutes on Days 1 and 8 of each 3-week cycle.	Safety PK
		E7389-J081-221	II	Patients with advanced or recurrent breast cancer previously treated with chemotherapy including an anthracycline and a taxane	84	Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle.	Response rate Safety
	Foreign	E7389-A001-101	I	Patients with advanced solid tumors	33	Eribulin mesilate was administered intravenously at 0.25, 0.5, 0.7, 1.0, or 1.4 mg/m^2 over 1 hour on Days 1, 8, and 15 of each 4-week cycle.	Safety PK
		E7389-A001-102		Patients with advanced solid tumors	21	Eribulin mesilate was administered intravenously at 0.25, 0.5, 1.0, 2.0, 2.8, or 4.0 mg/m^2 over 1 hour on Day 1 of each 3-week cycle.	Safety PK
		E7389-E044-103		Patients with advanced solid tumors	6	Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1[*1] and 8 of each 3-week cycle.	Safety PK
		E7389-E044-108		Patients with solid tumors (with normal hepatic function or mild or moderate hepatic impairment)	17	Eribulin mesilate was administered intravenously at the following doses over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle: Normal hepatic function, 1.4 mg/m^2; Mild hepatic impairment,[*2] 1.1 mg/m^2; Moderate hepatic impairment,[*2] 0.7 mg/m^2	Safety PK
		E7389-E044-109		Patients with advanced solid tumors	12	Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle (at 0.7 mg/m^2 when coadministered with ketoconazole).	Safety PK
		E7389-E044-110		Patients with advanced solid tumors	26	Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle	Safety [*3] PK
		E7389-A001-201	II	Patients with advanced or recurrent breast cancer previously treated with chemotherapy including an anthracycline and a taxane	104	Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 5 minutes on Days 1 and 8 of each 3-week cycle or on Days 1, 8, and 15 of each 4-week cycle.	Response rate Safety
		E7389-G000-211		Patients with advanced or recurrent breast cancer previously treated with 2 to 5 chemotherapy regimens including an anthracycline, a taxane, and capecitabine	299	Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle.	Response rate Safety PK
		E7389-G000-305	III	Patients with advanced or recurrent breast cancer previously treated with 2 to 5 chemotherapy regimens including an anthracycline and a taxane	762	Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle.	OS Safety
Reference data	Foreign	NCI-5730	I	Patients with advanced solid tumors	40	Eribulin mesilate was administered intravenously at 0.125, 0.25, 0.5, 0.7, 1.0, 1.4, or 2.0 mg/m^2 over 1 to 2 minutes on Days 1, 8, and 15 of each 4-week cycle.	Safety PK
		E7389-A001-202	II	Patients with advanced non-small cell lung cancer that progressed during or after platinum-based combination chemotherapy	106	Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle or on Days 1, 8, and 15 of each 4-week cycle.	Efficacy Safety
		E7389-G000-204		Patients with advanced or recurrent hormone-refractory prostate cancer	108	Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle.	Efficacy Safety

OS, overall survival; PK, pharmacokinetics;

[*1] ^{14}C-labeled eribulin acetate 2 mg (approximately 80-90 μCi) was administered on Day 1 of cycle 1;

[*2] The dose in patients with hepatic impairment could be increased up to 1.4 mg/m^2 if they met the standards for safety;

[*3] Electrocardiogram

Each clinical study is summarized below.

The major non-fatal adverse events reported in each clinical study are presented in "4.(iv) Adverse events and other relevant findings observed in clinical studies," and the PK-related study results are presented in "4.(ii) Summary of clinical pharmacology studies."

Evaluation data

4.(iii).A.(1) Japanese studies

4.(iii).A.(1).1) Japanese phase I study (5.3.3.2.3: Japanese Study E7389-J081-105, May 2006 to January 2008)

An open-label, uncontrolled study was conducted in patients with advanced solid tumors (target sample size, approximately 24 [3 to 6 per group]) at 1 center in Japan to determine the maximum tolerated dose* (MTD) and recommended dose and to evaluate the safety and tolerability of eribulin mesilate.

* As a rule, MTD was defined as the lowest dose level that induces DLT in ≥2 of 3 subjects or in ≥3 of 5 to 6 subjects in Cycle 1. However, when DLT was reported in 2 of 6 subjects, MTD was defined as the lowest dose level at which no further dose escalation was performed as recommended by the Efficacy and Safety Assessment Committee.

Eribulin mesilate was administered intravenously at 0.7, 1.0, 1.4, or 2.0 mg/m^2 over 2 to 10 minutes on Days 1 and 8 of each 3-week cycle. Treatment was continued unless the study discontinuation criteria were met.

All 15 enrolled subjects (3 in the 0.7 mg/m^2 group; 3 in the 1.0 mg/m^2 group, 6 in the 1.4 mg/m^2 group, and 3 in the 2.0 mg/m^2 group) received eribulin mesilate and were included in the safety analysis population.

DLT, the primary endpoint, occurred in 2 of 6 subjects in the 1.4 mg/m^2 group (febrile neutropenia and decreased neutrophil count in 1 subject; decreased neutrophil count in 1 subject) and in 3 of 3 subjects in the 2.0 mg/m^2 group (febrile neutropenia and decreased neutrophil count in 1 subject; decreased neutrophil count in 2 subjects) in Cycle 1. The MTD and recommended dose in the Japanese phase II study were determined to be 2.0 and 1.4 mg/m^2, respectively.

Safety results showed that no deaths occurred during the treatment period or within 30 days after the last dose of eribulin mesilate.

4.(iii).A.(1).2) Japanese phase II study (5.3.5.2.3: Japanese Study E7389-J081-221, January 2008 to September 2009)

An open-label, uncontrolled study was conducted in patients with advanced or recurrent breast cancer previously treated with chemotherapy including an anthracycline and a taxane (target sample size, 78-82) at 22 centers in Japan to evaluate the efficacy and safety of eribulin mesilate.

Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle. As a rule, subjects received ≥ 2 cycles of treatment with eribulin mesilate. They were allowed to continue treatment unless they met the study discontinuation criteria.

Of 84 enrolled subjects, 81 were included in the safety analysis population. The remaining 3 subjects did not receive eribulin mesilate. Of the 81 subjects, 80 were included in the full analysis set (FAS) and were subjected to the efficacy analysis. The remaining 1 subject withdrew from the study after receiving eribulin mesilate on Day 1 of Cycle 1, being found ineligible for the study (relapsed ≥1 year after postoperative adjuvant chemotherapy immediately before the study).

The primary efficacy endpoints were objective tumor response (best overall response as measured using the Response Evaluation Criteria in Solid Tumors [RECIST]) by independent review and overall response rate (the proportion of subjects with best overall response of CR or PR). The results of evaluations are shown in the table below.

Objective tumor response and overall response rate (best overall response by independent review)

Evaluation criteria (RECIST)	Number of subjects (%) (n = 80)
CR	0
PR	17 (21.3)
SD	30 (37.5)
PD	32 (40.0)
Not evaluable	1 (1.3)
Number of responding subjects (response rate)	17 (21.3)
[95% CI]	[12.9, 31.8]

Safety results revealed a death during the treatment period or within 30 days after the last dose of eribulin mesilate. The cause of the death was disease progression, and a causal relationship with eribulin mesilate was ruled out for the death.

4.(iii).A.(2) Foreign studies

4.(iii).A.(2).1) Foreign phase I study (5.3.3.2.1: Foreign Study E7389-A001-101, September 2003 to March 2005)

An open-label, uncontrolled study was conducted in patients with advanced solid tumors (target sample size, approximately 55) at 2 centers outside Japan to determine the MTD of eribulin mesilate.

Eribulin mesilate was administered intravenously at any of 11 dose levels specified within the range from 0.25 to 8.0 mg/m^2 over 1 hour on Days 1, 8, and 15 of each 4-week cycle. The treatment was continued unless the study discontinuation criteria were met. The initially scheduled 3-week cycle treatment was not carried out.

The dose was increased by 2 levels at an early stage of the study. Thereafter, the dose was increased by 1 level after the occurrence of a Grade ≥3 DLT or the occurrence of moderate or severe toxicity in 2 subjects. The study evaluated dose levels of 0.25, 0.5, 0.7, 1.0, and 1.4 mg/m^2.

Of 33 enrolled subjects, 32 (2 in the 0.25 mg/m^2 group, 8 in the 0.5 mg/m^2 group, 4 in the 0.7 mg/m^2 group, 9 in the 1.0 mg/m^2 group, 9 in the 1.4 mg/m^2 group) received eribulin mesilate and were included in the safety analysis population. The remaining 1 subject withdrew from the study because of rapid disease progression before starting study treatment.

The primary endpoint was MTD. DLT occurred in 1 of 8 subjects in the 0.5 mg/m^2 group (fatigue), 1 of 9 subjects in the 1.0 mg/m^2 group (fatigue and decreased appetite), and 5 of 9 subjects in the 1.4 mg/m^2 group (neutropenia in 4 subjects, and neutropenia and fatigue in 1 subject) in Cycle 1. The MTD of eribulin mesilate administered intravenously over 1 hour on Days 1, 8, and 15 of each 4-week cycle was determined to be 1.0 mg/m^2.

Safety results showed 3 deaths during the treatment period or within 30 days after the last dose of eribulin mesilate. The causes of the deaths were sepsis (1 subject in the 1.0 mg/m^2 group), disease progression (colorectal cancer; 1 subject in the 1.0 mg/m^2 group), and hypoxia associated with lung cancer (1 subject in the 1.4 mg/m^2 group). A causal relationship with eribulin mesilate was ruled out for all deaths.

4.(iii).A.(2).2) Foreign phase I study (5.3.3.2.2: Foreign Study E7389-A001-102, August 2003 to April 2005)

An open-label, uncontrolled study was conducted in patients with advanced solid tumors (target sample size, approximately 35) at 2 centers outside Japan to determine the MTD of eribulin mesilate.

Eribulin mesilate was administered intravenously at any of 11 dose levels specified within the range from 0.25 to 8.0 mg/m^2 over 1 hour on Day 1 of each 3-week cycle. The treatment was continued unless the study discontinuation criteria were met.

The dose was increased in the same manner as in Foreign Study E7389-A001-101. The dose levels examined in Foreign Study E7389-A001-102 were 0.25, 0.5, 1.0, 2.0, 2.8, and 4.0 mg/m^2.

All 21 enrolled subjects (1 in the 0.25 mg/m^2 group, 4 in the 0.5 mg/m^2 group, 3 in the 1.0 mg/m^2 group, 7 in the 2.0 mg/m^2 group, 3 in the 2.8 mg/m^2 group, 3 in the 4.0 mg/m^2 group) received eribulin mesilate and were included in the safety analysis population.

The primary endpoint was MTD. DLT occurred in 2 of 7 subjects in the 2.0 mg/m^2 group (febrile neutropenia and neutropenia in 1 subject each), 2 of 3 subjects in the 2.8 mg/m^2 group (febrile

neutropenia in 2 subjects), and 3 of 3 subjects in the 4.0 mg/m^2 group (febrile neutropenia in 3 subjects) in Cycle 1. The MTD of eribulin mesilate administered on Day 1 of each 3-week cycle was determined to be 2.0 mg/m^2.

Safety results showed a death in the 2.0 mg/m^2 group during the treatment period. The cause of the death was metastases to the brain. A causal relationship with eribulin mesilate was ruled out for the death.

4.(iii).A.(2).3) Foreign phase I study (5.3.3.2.4: Foreign Study E7389-E044-103, March 2009 to June 2009)

An open-label, uncontrolled study was conducted in patients with advanced solid tumors (maximum target sample size, 10) at 1 center outside Japan to investigate the elimination pathway of unchanged eribulin, the *in vivo* metabolic pathway, and the safety. The patients received a single intravenous dose of ^{14}C-eribulin administered over 2 to 5 minutes.

Each cycle consisted of 3 weeks. In Cycle 1, subjects received 2 mg of ^{14}C-labeled eribulin on Day 1 and 1.4 mg/m^2 of unlabeled eribulin intravenously over 2 to 5 minutes on Day 8. Thereafter, subjects were shifted to the extension phase, in which 1.4 mg/m^2 of unlabeled eribulin was given intravenously over 2 to 5 minutes on Days 1 and 8 of each cycle.

All 6 enrolled subjects received eribulin and were included in the safety analysis population.

Safety results showed no deaths during the main evaluation period (Cycle 1) in this study.

4.(iii).A.(2).4) Foreign phase I study (5.3.3.3.1: Foreign Study E7389-E044-108, February 2008 to March 2009)

An open-label, uncontrolled study was conducted in patients with advanced solid tumors who had normal hepatic function, mild hepatic impairment (Child-Pugh A), or moderate hepatic impairment (Child-Pugh B) (target sample size, 18 evaluable subjects) at 2 centers outside Japan, to investigate the effect of hepatic impairment on plasma eribulin PK parameters and the safety of eribulin mesilate given as a single dose.

Eribulin mesilate was administered intravenously over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle. In Cycle 1, 1.4 mg/m^2 was administered to subjects with normal hepatic function, 1.1 mg/m^2 to subjects with mild hepatic impairment, and 0.7 mg/m^2 to subjects with moderate hepatic impairment. From Cycle 2 onward, subjects with normal hepatic function were treated with the same dose as in Cycle 1, while subjects with mild or moderate hepatic impairment were allowed to increase their dose up to 1.4 mg/m^2 if they met the safety standards.

All 17 enrolled subjects (6 subjects with normal hepatic function, 7 subjects with mild hepatic impairment, and 4 subjects with moderate hepatic impairment) received eribulin mesilate and were included in the efficacy analysis population.

Safety results showed no deaths during the main evaluation period (Cycle 1) in the study.

4.(iii).A.(2).5) Foreign phase I study (5.3.3.4.1: Foreign Study E7389-E044-109, February 2009 to July 2009)

An open-label, uncontrolled study was conducted in patients with advanced solid tumors (target sample size, 12) at 1 center outside Japan to investigate the effect of repeated dose of concomitant oral ketoconazole, a CYP3A4 inhibitor, on the plasma pharmacokinetics and safety of eribulin mesilate.

Only in Cycle 1 (4 weeks), subjects received ketoconazole 200 mg twice daily on Days 15 and 16 or on Days 1 and 2. In this cycle, eribulin mesilate was administered intravenously over 2 to 5 minutes at 1.4 mg/m^2 when given alone or at 0.7 mg/m^2 when given in combination with ketoconazole. From Cycle 2 onward (1 cycle = 3 weeks), eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each cycle.

All 12 enrolled subjects received eribulin mesilate and were included in the safety analysis population.

Safety results showed no deaths during the main evaluation period (Cycle 1) in the study.

4.(iii).A.(2).6) Foreign phase I study (5.3.4.2.1: Foreign Study E7389-E044-110, February 2009 to July 2009)

An open-label, uncontrolled study was conducted in patients with advanced solid tumors (target sample size, 22 evaluable subjects) at 5 centers outside Japan to investigate the effect of eribulin mesilate on ECG, the QT/QTc interval in particular, and safety.

Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle.

Of 31 enrolled subjects with advanced solid tumors, 26 were included in the safety analysis population. The remaining 5 subjects were excluded from the analysis because they did not receive eribulin mesilate.

Safety results showed no deaths during the main evaluation period (Cycle 1) in the study.

4.(iii).A.(2).7) Foreign phase II study (5.3.5.2.1: Foreign Study E7389-A001-201, November 2004 to November 2006)

An open-label, uncontrolled study was conducted in patients with advanced or recurrent breast cancer previously treated with chemotherapy including an anthracycline and a taxane (target sample size, approximately 86) at 23 centers outside Japan, to investigate the efficacy and safety of monotherapy with eribulin mesilate.

Initially, eribulin mesilate was planned to be administered intravenously at 1.4 mg/m^2 over 5 minutes on Days 1, 8, and 15 of each 4-week cycle. However, postponed or suspended treatment, or dose reduction occurred in 41 of 70 subjects (58.6%) in Cycle 1 and 32 of 57 subjects (56.1%) in Cycle 2. Then the protocol was revised to change the dosage regimen to "intravenous administration at 1.4 mg/m^2 over 5 minutes on Days 1 and 8 of each 3-week cycle." The treatment was continued unless the study discontinuation criteria were met.

Of 104 enrolled subjects (71 in the 4-week cycle group and 33 in the 3-week cycle group), 103 (70 in the 4-week cycle group and 33 in the 3-week cycle group) were included in the intent-to-treat (ITT) population and the safety analysis population. The remaining 1 subject was excluded from the analyses because the subject did not receive eribulin mesilate. Of the 103 subjects, 87* (59 in the 4-week cycle group and 28 in the 3-week cycle group) were included in the per-protocol population (PPP) and the efficacy analysis population.

* These 87 subjects had (1) a measurable lesion according to RECIST at enrollment, (2) prior chemotherapy including an anthracycline and a taxane, and (3) disease progression confirmed within 6 months of the last dose of the most recent chemotherapy.

Overall response rates by independent review, the primary endpoint, are shown in the table below.

Objective tumor response and overall response rate, number of subjects (%) (PPP; by independent review)

Evaluation criteria (RECIST)	4-week cycle Number of subjects (%) (n = 59)	3-week cycle Number of subjects (%) (n = 28)	Total Number of subjects (%) (n = 87)
CR	0	0	0
PR	6 (10.2)	4 (14.3)	10 (11.5)
SD	21 (35.6)	16 (57.1)	37 (42.5)
PD	29 (49.2)	7 (25.0)	36 (41.1)
Unknown or missing data	3 (5.1)	1 (3.6)	4 (4.6)
Number of responding subjects (response rate) [95% CI]	6 (10.2) [3.8, 20.8]	4 (14.3) [4.0, 32.7]	10 (11.5) [5.7, 20.1]

Safety results showed that 7 deaths (5 subjects in the 4-week cycle group and 2 subjects in the 3-week cycle group) during the treatment period or within 30 days after the last dose of eribulin mesilate. The cause of the deaths was disease progression in all subjects, except for 1 subject in the 4-week cycle group who died of infection and disease progression. A causal relationship with eribulin mesilate was ruled out for the 6 subjects who died of disease progression, but could not be ruled out for the subject who died of infection and disease progression.

4.(iii).A.(2).8) Foreign phase II study (5.3.5.2.2: Foreign Study E7389-G000-211, October 2005 to September 2007)

An open-label, uncontrolled study was conducted in patients with advanced or recurrent breast cancer previously treated with 2 to 5 chemotherapy regimens including an anthracycline, a taxane, and capecitabine (target sample size, up to 300) at 80 centers outside Japan to investigate the efficacy and safety of eribulin mesilate.

Eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle. The treatment was continued unless the study discontinuation criteria were met.

Of 299 enrolled subjects, 291 were included in the ITT population and the safety analysis population. The remaining 8 subjects were excluded from the analysis for the following reasons: 1 subject was not registered in the database because of the loss of medical records at the study site; 7 subjects did not receive eribulin mesilate. Of the 291 subjects, 269 were included in the PPP and the efficacy analysis population. The remaining 22 subjects did not meet the inclusion criteria after enrollment.

Overall response rates by independent review, the primary endpoint, are shown in the table below.

Objective tumor response and overall response rate, number of subjects (%) (PPP; by independent review)

Evaluation criteria (RECIST)	Number of subjects (%) (n = 269)
CR	0
PR	25 (9.3)
SD	125 (46.5)
PD	116 (43.1)
Not evaluable	3 (1.1)
Number of responding subjects (response rate)	25 (9.3)
[95% CI]	[6.1, 13.4]

Safety results showed that 12 subjects died during the treatment period or within 30 days after the last dose of eribulin mesilate. The causes of the deaths were disease progression (including metastatic breast cancer) in 8 subjects and respiratory failure, stroke, carcinomatosis, and unknown (unexpected death) in 1 subject each. A causal relationship with eribulin mesilate could not be ruled out for the death of unknown cause (unexpected death).

4.(iii).A.(2).9) Foreign phase III study (5.3.5.1.1: Foreign Study E7389-G000-305, November 2006 to May 2009)

An open-label, randomized, comparative study was conducted in patients with advanced or recurrent breast cancer previously treated with 2 to 5 chemotherapy regimens including an anthracycline and a taxane (target sample size, up to 1000 in total; 667 in the eribulin mesilate group and 333 in the treatment

of the physician's choice [TPC] group) at 135 centers outside Japan, to compare eribulin mesilate with the TPC in terms of efficacy and safety.

In the eribulin mesilate group, eribulin mesilate was administered intravenously at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of each 3-week cycle. In the TPC group, subjects received any of the following treatments chosen by their attending physicians at enrollment: single-agent chemotherapy, hormonal therapy, or biological therapy approved in their own country (region) for the treatment of cancer; or palliative treatment or radiotherapy as standard care. Subjects were allowed to continue receiving eribulin mesilate or the TPC unless they met the study discontinuation criteria.

In the study, an interim analysis of overall survival (OS) was performed to evaluate the efficacy or inefficacy of treatment after 50% of the target number of deaths (206 deaths) had been reported. For the efficacy evaluation, the significance levels for the interim analysis and the final analysis were determined to be 0.003 and 0.049, respectively, based on the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function. In the inefficacy evaluation, if the lower limit of the 95% confidence interval for the hazard ratio was >0.85, the treatment was considered ineffective, and the study was to be discontinued.

All 762 enrolled subjects (508 in the eribulin mesilate group and 254 in the TPC group) were included in the ITT population. Of these, 750 subjects received treatment with eribulin mesilate or the TPC at least once (503 in the eribulin mesilate group and 247 in the TPC group), and they were included in the safety analysis population.

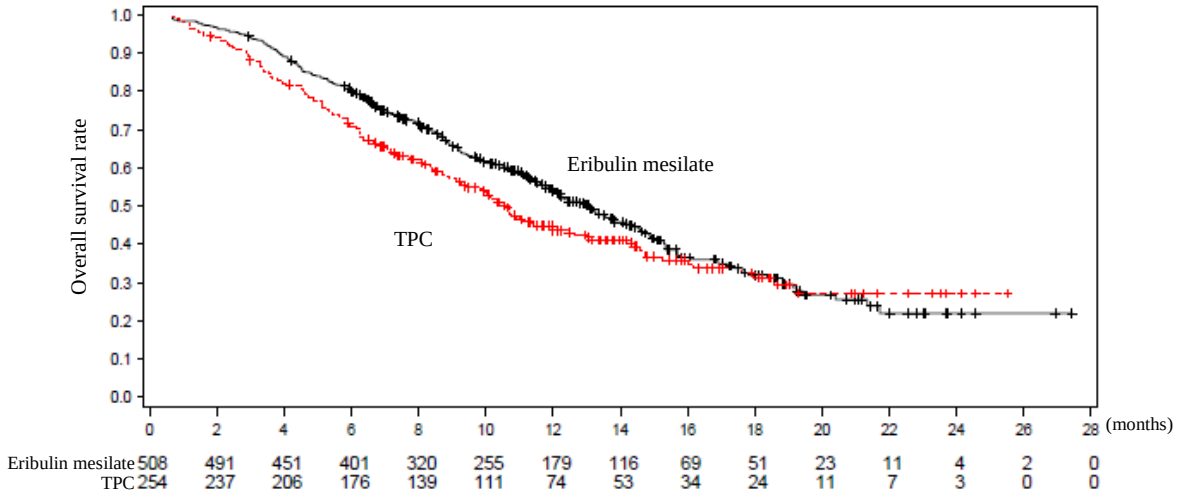
The primary endpoint of the study was OS, based on which the superiority of eribulin mesilate over TPC was investigated. The results of the final analysis of OS in each group are shown in the table below.

Results of the final analysis of OS (ITT population; data cut-off on May 12, 2009)

	Eribulin mesilate	TPC
ITT analysis population	508	254
Number of deaths (%)	274 (53.9)	148 (58.3)
Median OS (days) [95% CI]	399.0 [360.0, 434.0]	324.0 [282.0, 380.0]
Hazard ratio[*1] [95% CI]	0.809 [0.660, 0.991]	
P-value[*2]	0.041	

[*1] Stratified Cox proportional hazard model (stratified by HER2/neu status, prior capecitabine therapy, and geographical region)

[*2] Stratified log-rank test (stratified by HER2/neu status, prior capecitabine therapy, and geographical region)



Kaplan-Meier plots for OS (ITT population; data cut-off on May 12, 2009)

Safety results showed that 20 subjects in the eribulin mesilate group and 19 subjects in the TPC group died during the treatment period or within 30 days after the last study treatment. The causes of deaths in the eribulin mesilate group were disease progression in 11 subjects, dyspnea in 2 subjects, hypotension and febrile neutropenia resulting from septic shock, diabetic ketoacidosis, lung infection, pulmonary thromboembolism, respiratory failure due to disease progression, bronchopneumonia, and sepsis due to tumor infection in 1 subject each. A causal relationship with eribulin mesilate could not be ruled out for 5 of these events (disease progression,* dyspnea, febrile neutropenia, lung infection, and bronchopneumonia in 1 subject each). The causes of deaths in the TPC group were disease progression in 13 subjects, pulmonary embolism in 2 subjects, and invasive bronchopulmonary aspergillosis, pneumonia, respiratory failure, and asthenia due to clinical aggravation in 1 subject each. A causal relationship with the TPC could not be ruled out for 2 of these events (disease progression* and invasive bronchopulmonary aspergillosis in 1 subject each).

* Of subjects who died of "disease progression" as assessed by their own attending physicians, 1 subject in the eribulin mesilate group experienced dyspnea and 1 subject in the TPC group experienced febrile neutropenia. Because a causal relationship with the study drug could not be ruled out for these events, the applicant considered that the deaths of these subjects were possibly related to the study drug.

Reference data

4.(iii).A.(3).1) Foreign phase I study (5.3.3.2.7: Foreign Study NCI-5730, August 2002 to December 2005)

Eribulin mesilate was administered to all 40 patients enrolled in the study who had advanced solid tumors (1 in the 0.125 mg/m^2 group, 1 in the 0.25 mg/m^2 group, 7 in the 0.5 mg/m^2 group, 4 in the 0.7 mg/m^2 group, 3 in the 1.0 mg/m^2 group, 19 in the 1.4 mg/m^2 group, 5 in the 2.0 mg/m^2 group). No deaths were caused by eribulin mesilate-related adverse events.

4.(iii).A.(3).2) Foreign phase II study (5.3.5.4.1: Foreign Study E7389-A001-202, December 2004 to April 2006)

This study enrolled 106 patients with advanced non-small cell lung cancer (NSCLC) that progressed during or after platinum-based combination chemotherapy. Of the 106 patients, 103 (77 in the 4-week cycle group and 26 in the 3-week cycle group) received eribulin mesilate. A total of 14 subjects died during the treatment period or within 30 days after the last dose of eribulin mesilate. The causes of death were disease progression (including NSCLC, progression of NSCLC, lung cancer, and metastatic lung cancer) in 10 subjects, respiratory failure (including respiratory failure and lung cancer) in 3 subjects, and haemoptysis in 1 subject. A causal relationship with eribulin mesilate was ruled out for all events.

4.(iii).A.(3).3) Foreign phase II study (5.3.5.4.2: Foreign Study E7389-G000-204, February 2006 to May 2009)

Eribulin mesilate was administered to all 108 subjects enrolled in this study who had advanced or recurrent hormone-refractory prostate cancer. Two subjects died during the treatment period or within 30 days after the last dose of eribulin mesilate. The causes of death were disease progression in 1 subject and hypertension, gastrointestinal obstruction, bradycardia, and cardiac arrest in 1 subject. A causal relationship with eribulin mesilate was ruled out for all events.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Review policy

A phase III Foreign Study E7389-G000-305 enrolled patients with advanced or recurrent breast cancer who had a history of 2 to 5 chemotherapy regimens containing antineoplastic an anthracycline and a taxane. PMDA considered that the study yielded the most important data for the evaluation of efficacy and safety. PMDA therefore decided to focus its review on this study.

PMDA also decided to evaluate the efficacy and safety of eribulin mesilate in Japanese patients based primarily on the Japanese phase I and phase II studies (Japanese Studies E7389-J081-105 and E7389-J081-221).

4.(iii).B.(2) Efficacy

PMDA reviewed data from Foreign Study E7389-G000-305 (see the following subsections), and concluded that the efficacy of eribulin mesilate was demonstrated in patients with advanced or recurrent breast cancer who had received 2 to 5 prior chemotherapy regimens containing an antineoplastic anthracycline and an taxane.

4.(iii).B.(2).1) Selection of the control group

The applicant's rationale for selecting TPC as the control in Foreign Study E7389-G000-305:

No standard therapy has been established for third- or later-line treatment in patients with advanced or recurrent breast cancer previously treated with an anthracycline and a taxane. In clinical practice, a

treatment is chosen in light of the most recent chemotherapy, the patient's response and tolerability to the chemotherapy, the patient's preference, availability of drugs at the medical institution, and the patient's quality of life (QOL). In this situation, the TPC, including best supportive care (BSC), was chosen as the control in the study.

Furthermore, because therapeutic drug options for advanced or recurrent breast cancer keep changing drastically and the duration of Foreign Study E7389-G000-305 is as long as ≥18 months, it would be impractical to limit a control drug to ones that are available when Foreign Study E7389-G000-305 was being planned. For these reasons, the control patients should be allowed to use any of the TPC currently available for the third and subsequent line treatment for advanced or recurrent breast cancer, in order to evaluate the efficacy of eribulin mesilate.

PMDA's view:
Because the TPC includes various treatments, the results of Foreign Study E7389-G000-305 should be carefully interpreted. However, the individual TPCs in the study had no particular problems and were considered appropriate controls in the study. PMDA concluded that data from Foreign Study E7389-G000-305 is adequate for efficacy evaluation.

4.(iii).B.(2).2) Efficacy

In Foreign Study E7389-G000-305, the superiority of eribulin mesilate in OS over the TPC was evaluated based on the data cut-off on May 12, 2009 [see "4.(iii).A.(2).9) Foreign phase III study"]. The results of the follow-up analysis covering up to March 3, 2010 are presented in the table below, showing that the OS in the eribulin mesilate group was longer than that in the TPC group.

OS evaluation results (ITT population; data cut-off on March 3, 2010)

	Eribulin mesilate	TPC
ITT analysis population	508	254
Number of deaths (%)	386 (76.0)	203 (79.9)
Median OS (days) [95% CI]	403 [367, 438]	321 [281, 365]
Hazard ratio[*1] [95% CI]	0.805 [0.667, 0.958]	
P-value[*2]	0.014	

[*1] Stratified Cox proportional hazard model (stratified by HER2/neu status, prior capecitabine therapy, and geographical region)
[*2] Stratified log-rank test (stratified by HER2/neu status, prior capecitabine therapy, and geographical region)

Based on the above, PMDA concluded that the efficacy of eribulin mesilate was demonstrated in patients with advanced or recurrent breast cancer previously treated with chemotherapy including an anthracycline and a taxane.

In subgroup analyses of OS, eribulin mesilate was compared with drugs used in the TPC group after chemotherapy regimens including an anthracycline and a taxane (see the table below). PMDA confirmed that there was no notable bias in the efficacy of eribulin mesilate (i.e. hazard ratio of OS) between each TPC.

OS by treatment of the physician's choice (ITT population; data cut-off on May 12, 2009)

TPC	Number of deaths/number of subjects* TPC group	Hazard ratio [95% CI]
Capecitabine	24/45	0.716 [0.441, 1.163]
Vinorelbine ditartrate	40/65	0.620 [0.440, 0.874]
Gemcitabine hydrochloride	30/46	0.705 [0.474, 1.048]
Taxanes	19/41	1.311 [0.815, 2.110]
Anthracyclines	14/24	1.030 [0.596, 1.781]
Other	16/25	0.659 [0.390, 1.114]
Hormone therapy	5/8	1.083 [0.412, 2.848]

* In the eribulin mesilate group, the number of deaths/subjects was 274/508.

PFS was a secondary endpoint. PFS assessed by physicians was significantly longer in the eribulin mesilate group than in the TPC group (median PFS: eribulin mesilate, 110 days; TPC, 66 days; hazard ratio [95% CI], 0.757 [0.638, 0.900]; $P = 0.002$). PFS assessed by independent review tended to increase in the eribulin mesilate group, although there was no significant difference between the 2 groups (median PFS: eribulin mesilate, 113 days; TPC, 68 days; hazard ratio [95% CI], 0.865 [0.714, 1.048]; $P = 0.137$).

In Foreign Study E7389-G000-305, eribulin mesilate did not significantly prolong PFS assessed by independent review, despite significantly prolonging OS, as compared with TPC. PMDA asked the applicant to explain the reason for no significant prolongation of PFS in the eribulin mesilate group.

The applicant's response:
Because OS was the primary endpoint of this study, patients who had no target lesions that were evaluable by imaging were also allowed to participate in the study (40 of 508 subjects [7.9%] in the eribulin mesilate group and 40 of 254 subjects [15.7%] in the TPC group). The attending physicians of these subjects may diagnose disease progression, based on not only imaging but also clinical symptoms or laboratory findings. These subjects then may not undergo further diagnostic imaging and may start to receive new treatment. In the independent review, the day when the last evaluable imaging was taken or the imaging date immediately before starting new treatment is regarded as the day of censoring. This may cause a bias in the assessment.

In fact, among the ITT population in the study, the number of subjects censored for PFS was larger in the independent review (151 of 508 subjects [29.7%] in the eribulin mesilate group and 90 of 254 subjects [35.4%] in the TPC group) than in the attending physician-based assessment (79 of 508 subjects [15.6%] in the eribulin mesilate group and 48 of 254 subjects [18.9%] in the TPC group). These differences were considered to be the cause of no significant prolongation of PFS assessed by the independent review.

PMDA accepted the applicant's explanation on the reason for no significant prolongation of PFS (by the independent review) in the eribulin mesilate group, despite significantly prolonged OS as compared with the TPC group.

4.(iii).B.(2).3) Efficacy in Japanese patients

PMDA's view:

In the Japanese phase II study (Japanese Study E7389-J081-221) in patients with advanced or recurrent breast cancer previously treated with an anthracycline and a taxane, a certain level of clinical benefits was observed in the subjects receiving eribulin mesilate at the same dosing regimen as in Foreign Study E7389-G000-305. Therefore, eribulin mesilate is also expected be effective in Japanese patients based on the results of Foreign Study E7389-G000-305.

4.(iii).B.(3) Safety [for adverse events, see "4.(iv) Adverse events and other relevant findings observed in clinical studies"]

As a result of its review (see the following subsections), PMDA concluded that the adverse events requiring special attention during treatment with eribulin mesilate were bone marrow depression, peripheral nerve disorder, infections, hepatic function disorder, and interstitial lung disease. Despite these events, eribulin mesilate is tolerable as long as patients are followed appropriately by a physician with sufficient knowledge and experience in cancer chemotherapy through monitoring and controlling of adverse events and dose adjustment by reduction, or suspension or discontinuation of the drug. However, the applicant should collect and disseminate further post-marketing safety data, because limited data are currently available on the safety in Japanese patients, and because a comparison between Japanese and foreign studies has suggested higher incidences of Grade ≥3 adverse events in Japanese patients.

4.(iii).B.(3).1) Differences in the safety profile of eribulin mesilate between Japanese and non-Japanese patients

The applicant's explanation on differences in the safety profile of eribulin mesilate between Japanese and non-Japanese patients:

The table below shows adverse events that occurred at an incidence of ≥10% in Japanese Study E7389-J081-221 or 3 foreign studies (pooled analysis of the eribulin mesilate groups in Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305).

Adverse events with an incidence of ≥10% in Japanese Study E7389-J081-221 or foreign studies[*1] (number of subjects, %)

System Organ Class Preferred Term	Japanese Study E7389-J081-221 (n = 81)		Foreign studies (n = 827)	
	All grades	Grade 3-4	All grades	Grade 3-4
Number of subjects with AEs (incidence [%])	81 (100)	78 (96.3)	820 (99.2)	563 (68.1)
Blood and lymphatic system disorders	81 (100)	77 (95.1)	534 (64.6)	438 (53.0)
Anaemia	6 (7.4)	0	187 (22.6)	17 (2.1)
Febrile neutropenia	11 (13.6)	11 (13.6)	39 (4.7)	38 (4.6)
Leukopenia	80 (98.8)	60 (74.1)	186 (22.5)	116 (14.0)
Lymphopenia	44 (54.3)	10 (12.3)	19 (2.3)	7 (0.8)
Neutropenia	80 (98.8)	77 (95.1)	457 (55.3)	404 (48.9)
Gastrointestinal disorders	64 (79.0)	5 (6.2)	564 (68.2)	56 (6.8)
Constipation	13 (16.0)	0	229 (27.7)	8 (1.0)
Diarrhoea	15 (18.5)	0	165 (20.0)	6 (0.7)
Nausea	36 (44.4)	1 (1.2)	329 (39.8)	16 (1.9)

System Organ Class Preferred Term	Japanese Study E7389-J081-221 (n = 81)		Foreign studies (n = 827)	
	All grades	Grade 3-4	All grades	Grade 3-4
Stomatitis	32 (39.5)	2 (2.5)	75 (9.1)	6 (0.7)
Vomiting	16 (19.8)	1 (1.2)	170 (20.6)	11 (1.3)
General disorders and administration site conditions	67 (82.7)	5 (6.2)	621 (75.1)	118 (14.3)
Asthenia	4 (4.9)	0	247 (29.9)	54 (6.5)
Fatigue	37 (45.7)	1 (1.2)	273 (33.0)	32 (3.9)
Malaise	11 (13.6)	2 (2.5)	4 (0.5)	0
Mucosal inflammation	0	0	87 (10.5)	13 (1.6)
Oedema peripheral	5 (6.2)	0	90 (10.9)	4 (0.5)
Pain	9 (11.1)	2 (2.5)	61 (7.4)	12 (1.5)
Pyrexia	25 (30.9)	0	198 (23.9)	5 (0.6)
Infections and infestations	31 (38.3)	2 (2.5)	353 (42.7)	48 (5.8)
Nasopharyngitis	21 (25.9)	0	36 (4.4)	0
Urinary tract infection	0	0	89 (10.8)	5 (0.6)
Investigations	65 (80.2)	17 (21.0)	241 (29.1)	44 (5.3)
ALT increased	27 (33.3)	3 (3.7)	36 (4.4)	11 (1.3)
AST increased	30 (37.0)	6 (7.4)	33 (4.0)	10 (1.2)
Blood albumin decreased	10 (12.3)	1 (1.2)	1 (0.1)	0
Blood CPK increased	23 (28.4)	1 (1.2)	0	0
Blood glucose increased	12 (14.8)	0	0	0
Blood lactate dehydrogenase increased	16 (19.8)	1 (1.2)	11 (1.3)	2 (0.2)
C-reactive protein increased	14 (17.3)	0	1 (0.1)	1 (0.1)
γ-GTP increased	22 (27.2)	10 (12.3)	2 (0.2)	2 (0.2)
Haemoglobin decreased	28 (34.6)	5 (6.2)	6 (0.7)	1 (0.1)
Weight decreased	9 (11.1)	0	137 (16.6)	4 (0.5)
Blood ALP increased	17 (21.0)	3 (3.7)	15 (1.8)	3 (0.4)
Metabolism and nutrition disorders	47 (58.0)	6 (7.4)	319 (38.6)	56 (6.8)
Decreased appetite	38 (46.9)	1 (1.2)	206 (24.9)	6 (0.7)
Musculoskeletal and connective tissue disorders	32 (39.5)	0	464 (56.1)	63 (7.6)
Arthralgia	14 (17.3)	0	123 (14.9)	8 (1.0)
Back pain	5 (6.2)	0	126 (15.2)	15 (1.8)
Bone pain	0	0	88 (10.6)	15 (1.8)
Myalgia	8 (9.9)	0	98 (11.9)	3 (0.4)
Pain in extremity	3 (3.7)	0	97 (11.7)	9 (1.1)
Nervous system disorders	50 (61.7)	4 (4.9)	503 (60.8)	93 (11.2)
Dizziness	9 (11.1)	0	73 (8.8)	3 (0.4)
Dysgeusia	27 (33.3)	–*2	82 (9.9)	–*2
Headache	13 (16.0)	0	169 (20.4)	6 (0.7)
Neuropathy peripheral	2 (2.5)	0	113 (13.7)	25 (3.0)
Paraesthesia	1 (1.2)	0	90 (10.9)	13 (1.6)
Peripheral sensory neuropathy	19 (23.5)	3 (3.7)	94 (11.4)	14 (1.7)
Respiratory, thoracic, and mediastinal disorders	26 (32.1)	3 (3.7)	344 (41.6)	49 (5.9)
Cough	13 (16.0)	1 (1.2)	136 (16.4)	4 (0.5)
Dyspnoea	4 (4.9)	1 (1.2)	144 (17.4)	34 (4.1)
Skin and subcutaneous tissue disorders	54 (66.7)	1 (1.2)	483 (58.4)	5 (0.6)
Alopecia	47 (58.0)	–*2	417 (50.4)	–*2
Rash	11 (13.6)	0	49 (5.9)	1 (0.1)

*1 Pooled analysis of the eribulin mesilate groups in Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305; *2 Because the CTCAE v. 3.0 does not define severities of Grade ≥3 of the relevant adverse event, neither the number of subjects nor the incidence are presented in these cells.

The incidences of the following adverse events were higher in Japanese subjects than in non-Japanese subjects: leukopenia, neutropenia, lymphopenia, and abnormalities in laboratory test values (mainly, alanine aminotransferase [ALT] increased, haemoglobin decreased, aspartate aminotransferase [AST] increased, blood creatine phosphokinase increased, gamma-glutamyl transpeptidase increased, and blood alkaline phosphatase [ALP] increased). The incidences of these events that were Grade ≥3 in severity were also higher in Japanese subjects than in non-Japanese subjects. However, differences in

the incidences of leukopenia, neutropenia, lymphopenia, and abnormalities in laboratory test values between Japanese and non-Japanese subjects are likely attributable to differences in laboratory parameters and the methods of assessment of adverse events based on laboratory values.

PMDA asked the applicant to compare adverse events reported in Japanese Study E7389-J081-221 and foreign studies (pooled analysis of the eribulin mesilate groups in Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305) and to explain the reason for higher incidences of some adverse events (other than blood and lymphatic system disorders and abnormalities in laboratory values) in Japanese Study E7389-J081-221 than in the foreign studies.

The applicant's response:
The following adverse events showed a ≥10 % higher incidence in Japanese Study E7389-J081-221 than in the foreign studies: stomatitis, decreased appetite, dysgeusia, nasopharyngitis, fatigue, malaise, and peripheral sensory neuropathy.

Differences in the incidences of stomatitis, decreased appetite, and dysgeusia between Japanese and non-Japanese subjects were primarily attributable to the differences in the incidences of Grade 1 events (see the table below). This may indicate the possibility that Japanese physicians collected data on events of low severity more meticulously than non-Japanese physicians did. However, there is no evidence exactly explaining these differences. Therefore, the fact that stomatitis, decreased appetite, and dysgeusia were reported more frequently from Japanese subjects than non-Japanese subjects will be communicated to healthcare professionals using suitable materials.

Incidences of stomatitis, decreased appetite, and dysgeusia in Japanese Study E7389-J081-221 and foreign studies[*1] (number of subjects; %)

System Organ Class Preferred Term	Japanese Study E7389-J081-221 (n = 81)				Foreign studies (n = 827)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis	26 (32.1)	4 (4.9)	2 (2.5)	0	45 (5.4)	24 (2.9)	6 (0.7)	0
Decreased appetite	30 (37.0)	7 (8.6)	1 (1.2)	0	130 (15.7)	70 (8.5)	6 (0.7)	0
Dysgeusia	22 (27.2)	5 (6.2)	–[*2]	–[*2]	67 (8.1)	15 (1.8)	–[*2]	–[*2]

[*1] Pooled analysis of the eribulin mesilate groups in Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305; [*2] Because the CTCAE v. 3.0 does not define severities of Grade ≥3 of dysgeusia, neither the number of subjects nor the incidence are presented in these cells.

The reason for the difference in the incidence of nasopharyngitis between Japanese and non-Japanese subjects is unclear. However, most events of nasopharyngitis were assessed as unrelated to eribulin mesilate and none of the events were Grade ≥3 in severity. The difference in the incidence is therefore unlikely to be clinically significant.

The differences in the incidences of fatigue and malaise are considered attributable to the choice of event terms reported. The total incidence of asthenia, fatigue, and malaise was 52 of 81 subjects (64.2%) in Japanese Study E7389-J081-221 and 495 of 827 subjects (59.9%) in non-Japanese studies, showing little difference.

The difference in the incidence of peripheral sensory neuropathy is also considered attributed to the choice of event terms reported. The total incidence of adverse events related to peripheral nerve disorders including peripheral sensory neuropathy was 22 of 81 subjects (27.2%) in Japanese Study E7389-J081-221 and 289 of 827 subjects (34.9%) in foreign studies, showing little difference.

PMDA's view on ethnic differences in the safety profile of eribulin mesilate:
The sample size of Japanese subjects for eribulin mesilate safety evaluation was smaller than that of non-Japanese subjects, and this precluded an accurate comparison of the safety profile between these populations. Nevertheless, the differences between Japanese and non-Japanese subjects in the incidences of leukopenia, neutropenia, lymphopenia, abnormalities in laboratory values (e.g., ALT increased, haemoglobin decreased), stomatitis, decreased appetite, and dysgeusia should be communicated to healthcare professionals in an appropriate manner though written materials.

4.(iii).B.(3).2) Bone marrow depression

The applicant's explanation on bone marrow depression observed in subjects treated with eribulin mesilate:
The following are bone marrow depression-related events observed in Japanese Study E7389-J081-221: white blood cell decreased in 80 of 81 subjects (98.8%), neutrophil count decreased in 80 of 81 subjects (98.8%), lymphocyte count decreased in 44 of 81 subjects (54.3%), anaemia in 34 of 81 subjects (42.0%), and platelets decreased in 9 of 81 subjects (11.1%). Among these, Grade 3 or 4 events were white blood cell decreased in 60 of 81 subjects (74.1%), neutrophil count decreased in 77 of 81 subjects (95.1%), lymphocyte count decreased in 10 of 81 subjects (12.3%), and anaemia in 5 of 81 subjects (6.2%). There were no Grade 3 or 4 platelets decreased.

In the 3 foreign studies (pooled analysis of the eribulin mesilate groups in Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305), the following events related to bone marrow depression were observed: white blood cell decreased in 192 of 827 subjects (23.2%), neutrophil count decreased in 481 of 827 subjects (58.2%), lymphocyte count decreased in 19 of 827 subjects (2.3%), anaemia in 191 of 827 subjects (23.1%), and platelets decreased in 27 of 827 subjects (3.3%). Among these, Grade 3 or 4 events were white blood cell decreased in 119 of 827 subjects (14.4%), neutrophil count decreased in 424 of 827 subjects (51.3%), lymphocyte count decreased in 7 of 827 subjects (0.8%), anaemia in 18 of 827 subjects (2.2%), and platelets decreased in 9 of 827 subjects (1.1%).

Because bone marrow depression-related adverse events occurred frequently in the Japanese study, patients should be carefully monitored for infection through frequent blood tests or other means in the post-marketing setting. If any abnormality is detected, appropriate measures should be taken, such as dose delay (if the patient does not meet criteria for the start of treatment on Day 1 of each cycle) or dose reduction or suspension (if the patient does not meet criteria for the start of treatment on Day 8 of each cycle). The use of granulocyte colony-stimulating factors (G-CSFs) or antibiotics should be considered as needed.

PMDA's view on bone marrow depression observed in subjects treated with eribulin mesilate:
Eribulin mesilate is considered tolerable as long as patients are followed appropriately through monitoring and controlling of adverse events, dose reduction, or suspension or discontinuation of the treatment by a physician with sufficient knowledge and experience in cancer chemotherapy. However, because of frequent bone marrow depression in subjects receiving eribulin mesilate, patients should be carefully monitored during treatment by regular blood tests or other means. The applicant should appropriately inform healthcare professionals of actions to be taken following the detection of bone marrow depression during treatment with eribulin mesilate, along with the criteria for dose reduction and the suspension or discontinuation of treatment.

4.(iii).B.(3).3) Peripheral nerve disorder

The applicant's explanation on peripheral nerve disorder observed in subjects treated with eribulin mesilate:
Taxanes and other anticancer drugs that act on microtubules may induce a peripheral nerve disorder, which has been highlighted as one of adverse events that may lead to the discontinuation of treatment. Eribulin mesilate, a drug acting on microtubules, is also suspected to induce a peripheral nerve disorder.

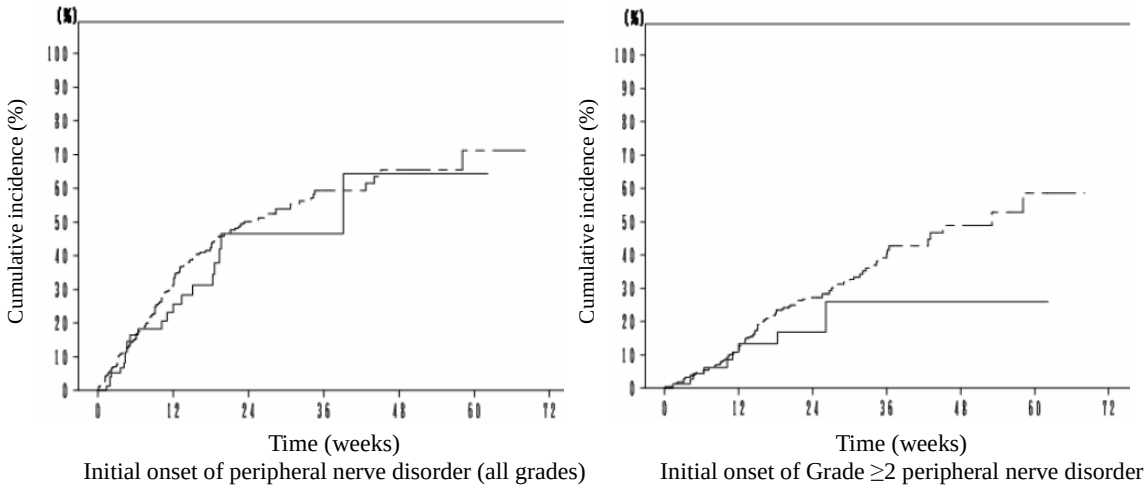
In Japanese Study E7389-J081-221, peripheral nerve disorder was reported in 22 of 81 subjects (27.2%). The events in 3 of 81 subjects (3.7%) were Grade 3 or 4 in severity.

In the 3 foreign studies (pooled analysis of the eribulin mesilate groups in Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305), peripheral nerve disorder occurred in 289 of 827 subjects (34.9%). The events in 63 of 827 subjects (7.6%) were Grade 3 or 4 in severity.

The foreign studies reported relatively frequent Grade 3 or 4 peripheral nerve disorder including some serious adverse drug reactions. Therefore, patients should be carefully monitored for the event during treatment with eribulin mesilate.

PMDA asked the applicant to explain the possibility that prolonged use of eribulin mesilate may increase the incidence of high-grade peripheral nerve disorder (potential accumulation of toxicity) and the safety of eribulin mesilate in patients with a history of peripheral nerve disorder caused by prior treatment.

The applicant's explanation:
The results of Japanese and foreign studies showed that the cumulative incidence of peripheral nerve disorder increased with prolonged treatment with eribulin mesilate. After a certain treatment period, however, there was no tendency toward rapid increase in the incidence of peripheral nerve disorder or high-grade peripheral nerve disorder (see the figure below). Eribulin mesilate is therefore considered to cause no accumulation of toxicity.



Kaplan-Meier plots for the initial onset of peripheral nerve disorder
(solid lines, Japanese Study E7389-J081-221; dotted lines, foreign studies [pooled analysis of Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305])

Similarly, Japanese and foreign studies did not suggest a tendency toward an earlier onset of, higher susceptibility to, or higher grade of peripheral nerve disorder after treatment with eribulin mesilate in patients who had peripheral nerve disorder at baseline (see the table below). Eribulin mesilate is therefore considered usable also in patients with a history of peripheral nerve disorder caused by previous treatment(s), provided that patients are carefully monitored and, adequate measures, such as dose reduction or suspension, are taken in case of numbness and other relevant symptoms.

Incidence of peripheral nerve disorder by baseline grade of the event in Japanese Study E7389-J081-221 (number of subjects; %)

Baseline grade	Number of subjects	Peripheral nerve disorder by grade				
		All grades	Grade 1	Grade 2	Grade 3	Grade 4
Grade 0	49	16 (32.7)	12 (24.5)	3 (6.1)	1 (2.0)	0
Grade 1	32	6 (18.8)	1 (3.1)	3 (9.4)	2 (6.3)	0
Grade ≥2	0	0	0	0	0	0

In subjects who had peripheral nerve disorder at baseline, new onset or worsening of peripheral nerve disorder after the beginning of eribulin therapy was counted as an adverse event.

Incidence of peripheral nerve disorder by baseline grade of the event in Foreign Studies E7389-G000-211 and E7389-G000-305 (number of subjects; %)

Baseline grade	Number of subjects	Peripheral nerve disorder by grade				
		All grades	Grade 1	Grade 2	Grade 3	Grade 4
Grade 0	625	212 (33.9)	111 (17.8)	55 (8.8)	44 (7.0)	2 (0.3)
Grade 1	142	55 (38.7)	14 (9.9)	27 (19.0)	14 (9.9)	0
Grade ≥2*	27	9 (33.3)	4 (14.8)	2 (7.4)	3 (11.1)	0

In subjects who had peripheral nerve disorder at baseline, new onset or worsening of peripheral nerve disorder after the beginning of eribulin therapy was counted as an adverse event.
* Grade ≥3 peripheral nerve disorder was an exclusion criterion in these studies.

PMDA's view on peripheral nerve disorder caused by eribulin mesilate:

The Japanese and foreign studies reported serious peripheral nerve disorder. It required a maximum of 479 days after the discontinuation of eribulin mesilate to resolve or never resolved. The incidences and outcomes of peripheral nerve disorder should be adequately communicated to healthcare professionals using written materials.

At present, eribulin mesilate is not considered to have a risk of cumulative toxicity due to peripheral nerve disorder or safety concerns in patients with Grade ≤2 peripheral nerve disorder caused by previous treatment(s). However, eribulin mesilate should be carefully administered based on the risk-benefit balance in individual patients, and dose reduction, treatment suspension or other appropriate measures should be taken as needed. New findings from post-marketing data should be promptly provided to healthcare professionals.

4.(iii).B.(3).4) Infections

The applicant's explanation on infections (events classified into "infections and infestations" by System Organ Class) observed in subjects treated with eribulin mesilate:

In Japanese Study E7389-J081-221, infections occurred in 31 of 81 subjects (38.3%) and Grade 3 infections in 2 of 81 subjects (2.5%).

In the 3 foreign studies (pooled analysis of the eribulin mesilate groups in Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305), infections occurred in 353 of 827 subjects (42.7%) and Grade ≥3 infections in 48 of 827 subjects (5.8%). Bronchopneumonia, sepsis, and lung infection resulted in death in 1 subject (0.1%) each. A causal relationship with eribulin mesilate could not be ruled out for bronchopneumonia and lung infection.

Life-threatening infections (e.g., urinary tract infection, sepsis, and pneumonia) were caused by eribulin mesilate-induced bone marrow depression. Appropriate measures, including the proper use of antibiotics, confirmation of recovery from infection before resuming the treatment, and dose reduction, should be taken.

PMDA's view on infections observed during treatment with eribulin mesilate:

Decreased white blood cells, neutrophils, and lymphocytes were observed following treatment with eribulin mesilate. Patients experiencing these events during treatment with eribulin mesilate may become susceptible to infections. Therefore, patients receiving eribulin mesilate should be carefully monitored for infections, parasitosis, and febrile neutropenia such as by regular blood tests.

4.(iii).B.(3).5) Hepatic function disorder

The applicant's explanation on hepatic function disorder (hepatic function abnormal, hepatitis, hepatitis acute, hepatotoxicity, liver disorder, liver function test abnormal, cytolytic hepatitis, and transaminases increased) observed during treatment with eribulin mesilate:

In Japanese Study E7389-J081-221, hepatic function disorder occurred in 7 of 81 subjects (8.6%). No subject experienced Grade ≥3 hepatic function disorder.

In the 3 foreign studies (pooled analysis of the eribulin mesilate groups in Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305), hepatic function disorder occurred in 16 of 827 subjects (1.9%). Grade 3 hepatic function disorder occurred in 8 of 827 subjects (1.0%). Serious adverse events were cytolytic hepatitis in 1 of 827 subjects (0.1%) and liver function test abnormal leading to the discontinuation of eribulin mesilate in 1 of 827 subjects (0.1%).

Japanese and foreign studies have reported markedly abnormal laboratory values related to liver function, although they were infrequent. As of [redacted], 20[redacted], a foreign study has reported hepatic failure in 1 subject and hepatitis toxic resulting in death in 1 subject, although the study is not included in the clinical data package for the present application. A causal relationship with eribulin mesilate could not be ruled out for these events.

As above, hepatic function disorder occurred in Japanese and foreign studies, and a causal relationship with eribulin mesilate cannot be ruled out for some fatal events in a foreign study. Therefore, hepatic function disorder requires special attention.

PMDA's view on hepatic function disorder observed during treatment with eribulin mesilate:
Using the package insert, etc., the applicant should appropriately inform healthcare professionals that eribulin mesilate induced hepatic function disorder in Japanese and foreign studies, with especially serious events in foreign studies.

4.(iii).B.(3).6) Interstitial lung disease

The applicant' explanation on interstitial lung disease observed during treatment with eribulin mesilate:
In Japanese Study E7389-J081-221, Grade 4 interstitial lung disease was reported in 1 subject on Day 38 of Cycle 4. The subject was diagnosed with interstitial pneumonia by the investigator because of the following findings: (1) cancer metastasis and infections were excluded; (2) the subject responded to steroid pulse therapy; and (3) imaging findings and other data. Interstitial pneumonia improved slightly after steroid pulse therapy, but the subject did not recover and died from rapid liver metastasis.

In Foreign Study E7389-G000-211, Grade 2 interstitial lung disease (verbatim term: lung disorder) was reported in 1 subject on Day 3 of Cycle 4. The event was resolved by multiple antibiotics. A causal relationship with eribulin mesilate could not be ruled out for the event.

As above, interstitial pneumonia occurred after the administration of eribulin mesilate in Japanese and foreign studies, although infrequently. Patients should therefore be carefully monitored for a sign of the event through chest radiography and other relevant examinations. Eribulin mesilate should be discontinued or other appropriate measure should be taken in case of any abnormal changes.

PMDA's view on interstitial lung disease observed during treatment with eribulin mesilate:
At present, because of the limited number of patients, the incidence of interstitial pneumonia after treatment with eribulin mesilate is unknown. However, a subject receiving eribulin mesilate in the

Japanese study had interstitial lung disease and died without recovering from the event. This information should be communicated to healthcare professionals through the package insert, etc.

Post-marketing safety data on interstitial lung disease should be collected. Based on the collected data, additional precautionary advice should be given to healthcare professionals or other corrective actions should be taken promptly and appropriately as necessary.

4.(iii).B.(4) Clinical positioning and indication

The proposed indication for eribulin mesilate is "inoperable or recurrent breast cancer." The following information is planned to be included in the "Precautions for Indication" section:

- The efficacy and safety of eribulin mesilate for adjuvant or neoadjuvant chemotherapy have not been established.
- Eribulin mesilate is indicated for patients with breast cancer that has worsened or recurred after chemotherapy including an anthracycline and a taxane.
- The efficacy and safety of eribulin mesilate combined with other antitumor drugs have not been established.

PMDA asked the applicant to explain the clinical positioning of eribulin mesilate in the treatment of advanced or recurrent breast cancer.

The applicant's explanation:

In the treatment for advanced or recurrent breast cancer, anthracyclines and taxanes are used for the first-line therapy, and second-line drugs are selected from other available first-line drugs that have not been used in the patient. All these drugs are standard therapies. In Japan, the third-line therapies after a chemotherapy with an anthracycline and a taxane include capecitabine, tegafur-gimeracil-oteracil potassium combination, vinorelbine ditartrate, etc. However, none of these drugs are regarded as standard therapies because of lack of evidence.

Foreign Study E7389-G000-305 demonstrated the efficacy and safety of eribulin mesilate as third- and later-line therapies. Eribulin mesilate is thus expected to be a first treatment option for patients with advanced or recurrent breast cancer previously treated with chemotherapy including an anthracycline and a taxane.

PMDA's view on the clinical positioning of eribulin mesilate:

For the following 2 reasons, eribulin mesilate has a potential to be a first therapeutic option for patients with advanced or recurrent breast cancer previously treated with 2 to 5 chemotherapies including an anthracycline and a taxane: (a) the clinical benefits of eribulin mesilate in the mentioned patient population have been demonstrated [see "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety"]; and (b) currently, no drugs have been established as standard third-line therapies. At present, a foreign phase III comparative study (Foreign Study E7389-G000-[redacted]) is ongoing in patients with advanced or recurrent

breast cancer previously treated with chemotherapy including an anthracycline and a taxane, to compare the efficacy and safety of eribulin mesilate and [redacted]. Data from the study will help clarify (1) the clinical positioning of eribulin mesilate and (2) when to use eribulin mesilate or other antineoplastic agents in the mentioned patient population.

PMDA's conclusion:
Eribulin mesilate is a therapeutic option for patients with inoperable or recurrent breast cancer. The indication should be "inoperable or recurrent breast cancer" as proposed by the applicant. The following information should be included in the "Precautions for Indication" section of the package insert:

- The efficacy and safety of eribulin mesilate for adjuvant or neoadjuvant chemotherapy have not been established.
- Eribulin mesilate is indicated for patients with breast cancer that has worsened or recurred after chemotherapy including an anthracycline and a taxane.

PMDA also concluded that precautionary advice on the use of eribulin mesilate in combination with other antitumor drugs should be presented in the "Precautions for Dosage and Administration" section [see "4.(iii).B.(5).4) Use of eribulin mesilate in combination with other antineoplastic agents"].

4.(iii).B.(5) Dosage and administration

PMDA discussed dosage and administration of eribulin mesilate (see the following subsections), and concluded that the dosage and administration in patients with advanced or recurrent breast cancer previously treated with chemotherapy including an anthracycline and a taxane should be as follows: "The usual adult dosage is 1.4 mg/m^2 (body surface area) of eribulin mesilate administered intravenously over 2 to 5 minutes at 1 week interval for 2 consecutive weeks, followed by a rest week. This treatment cycle is repeated. The dose may be adjusted according to the patient's condition." PMDA also concluded that the following information should be presented in the "Precautions for Dosage and Administration" section.

- A note that the efficacy and safety of eribulin mesilate in combination with other antitumor drugs have not been established.
- Criteria for dose delay, reduction, suspension, and discontinuation
- Precautionary advice for the use of eribulin mesilate in patients with hepatic impairment

4.(iii).B.(5).1) Dosage and administration

The applicant's rationale for the dosage and administration of eribulin mesilate:
In the 3 foreign phase I studies (Foreign Studies NCI-5730, E7389-A001-101, and E7389-A001-102), the dosing regimen of eribulin mesilate was explored. The recommended dose (1.4 mg/m^2) yielded the highest dose intensity (1.05, 0.75, and 0.67 mg/m^2/week in Foreign Studies NCI-5730, E7389-A001-101, and E7389-A001-102, respectively). The following dosing regimen was well tolerated in Foreign Study NCI-5730, and was then selected as the recommended dosing regimen for the foreign phase II study (Foreign Study E7389-A001-201) and subsequent studies: "Eribulin mesilate is administered

intravenously at 1.4 mg/m^2 on Days 1, 8, and 15 of each 4-week cycle." However, many subjects in Foreign Study E7389-A001-201 experienced neutropenia leading to dose delay, reduction, or suspension during Cycle 1 or 2 (41 of 70 subjects [58.6%] in Cycle 1 and 32 of 57 subjects [56.1%] in Cycle 2). The recommended dosing regimen was therefore modified as follows: "Eribulin mesilate is administered intravenously at 1.4 mg/m^2 on Days 1 and 8 of each 3-week cycle." Since the modified regimen of eribulin mesilate showed an acceptable safety profile, it was used in the subsequent foreign studies. Foreign phase II and III studies (Foreign Studies E7389-G000-211 and E7389-G000-305) demonstrated the efficacy and safety of the 3-week cycle regimen of eribulin mesilate in patients with advanced or recurrent breast cancer previously treated with chemotherapy including an anthracycline and a taxane. A Japanese phase I study (Japanese Study E7389-J081-105) verified the tolerability of the 3-week cycle regimen of eribulin mesilate, and a Japanese phase II study (Japanese Study E7389-J081-221) demonstrated a certain level of clinical effectiveness of the regimen.

Accordingly, the dosage and administration statement was established for use in Japan.

PMDA's conclusion:
The applicant's rationale for the proposed dosage and administration is generally acceptable. However, the rationale for dosing time of "2 to 5 minutes" remains unclear. The wording of dosage and administration should therefore be reconsidered [see "4.(ii).B.(3) Duration of intravenous infusion"].

4.(iii).B.(5).2) Criteria for dose reduction, suspension and discontinuation of eribulin mesilate

The applicant's explanation on the criteria for dose reduction, and suspension and discontinuation of eribulin mesilate:
As shown in the table below, there were some differences in criteria for dose reduction, suspension, and discontinuation of eribulin mesilate between Foreign Study E7389-G000-305 and Japanese Study E7389-J081-221. These differences, however, were minor. The present application includes foreign study data, supported by the efficacy and safety profiles of eribulin mesilate confirmed in Japanese Study E7389-J081-221. Therefore, the dose reduction criteria to be presented in the package insert should be the one used in Japanese Study E7389-J081-221.

Dose reduction criteria of eribulin mesilate in Foreign Study E7389-G000-305 and Japanese Study E7389-J081-221

Foreign Study E7389-G000-305	Japanese Study E7389-J081-221
Dose in the previous cycle → Reduced dose	Dose in the previous cycle → Reduced dose
1.4 mg/m^2 → 1.1 mg/m^2 1.1 mg/m^2 → 0.7 mg/m^2 0.7 mg/m^2 → Consider discontinuation of eribulin mesilate	1.4 mg/m^2 → 1.2 mg/m^2 1.2 mg/m^2 → 1.0 mg/m^2 1.0 mg/m^2 → 0.7 mg/m^2 0.7 mg/m^2 → Consider discontinuation of eribulin mesilate

PMDA asked the applicant to explain how and why the dose reduction criteria of eribulin mesilate in Japanese Study E7389-J081-221 were different from those in Foreign Study E7389-G000-305.

The applicant's explanation:

In Foreign Study E7389-G000-305, the starting dose was 1.4 mg/m^2, and reduced doses were 80% (1.1 mg/m^2) and 50% (0.7 mg/m^2) of the starting dose.

For Japanese Study E7389-J081-221, the doses were determined from the viewpoint of safety in subjects, based on the results of Japanese Study E7389-J081-105, which demonstrated the tolerability of eribulin mesilate in Japanese patients with solid tumors. Initially, the dose was planned to be reduced from the starting dose of 1.4 mg/m^2 to either one of 2 doses (0.7 and 1.0 mg/m^2) that had been proven to be tolerable. However, the percentage of reduction from 1.4 mg/m^2 to 1.0 mg/m^2 was greater than from 1.4 mg/m^2 to 1.1 mg/m^2 as a standard in the foreign phase III study; the reduction to 1.0 mg/m^2 raised concerns about reduced efficacy. Therefore, the 1.2 mg/m^2 dose (an intermediate dose between 1.4 and 1.0 mg/m^2) was also used so that the dose would be adjusted more gradually (1.4 mg/m^2 → 1.2 mg/m^2 → 1.0 mg/m^2 → 0.7 mg/m^2).

PMDA's view on the criteria for dose reduction, suspension and discontinuation of eribulin mesilate:
In Japanese Study E7389-J081-221, only a small number of subjects (27 of 84 subjects; 32.1%) were treated with a reduced dose. The efficacy and safety of eribulin mesilate were verified in Foreign Study E7389-G000-305. Given these, the available data do not provide convincing evidence for the applicant's claim that the dose adjustment criteria in Japanese Study E7389-J081-221 were more appropriate than those in Foreign Study E7389-G000-305. Therefore, the dose adjustment criteria in Foreign Study E7389-G000-305 should also be communicated to healthcare professionals through the package insert and other written materials, along with those in Japanese Study E7389-J081-221, as guidelines for dose reduction, suspension, and discontinuation of eribulin mesilate.

4.(iii).B.(5).3) Use in patients with hepatic impairment [see "4.(ii).B.(4) Use in patients with hepatic impairment"]

Based on the description in "4.(ii).B.(4) Use in patients with hepatic impairment," PMDA considers that physicians should carefully determine eligibility for eribulin mesilate when treating a patient with hepatic impairment because he/she may have another complication or reduced physical status.

Furthermore, the following findings should be appropriately provided to healthcare professionals using written materials.

- In Japanese and foreign studies to investigate the efficacy and safety of eribulin mesilate (Japanese Study E7389-J081-221 and Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305), the hepatic function-related eligibility criteria were as follows: total bilirubin of ≤1.5-fold the upper limit of historical data of the study site, and AST and ALT of ≤2.5-fold the upper limit of historical data of the study site (≤5.0-fold in patients with liver metastasis). The incidence of Grade 4 neutropenia may increase in patients with total bilirubin of 1- to 1.5-fold the upper limit of historical data of the study site or AST or ALT of 2.5- to 5.0-fold the upper limit of historical data of the study site.

- Because the patient's hepatic function affects the pharmacokinetics of eribulin, the incidence of Grade 4 neutropenia may increase in patients with hepatic impairment who receive eribulin mesilate.

4.(iii).B.(5).4) Use of eribulin mesilate in combination with other antineoplastic agents

In the clinical studies contained in the submitted data, eribulin mesilate was administered alone irrespective of the expression status of human epidermal growth factor receptor 2 (HER2) in subjects. PMDA asked the applicant to explain the use of eribulin mesilate in combination with other antitumor drugs.

The applicant's explanation:

Patients with advanced or recurrent HER2/neu-positive breast cancer previously treated with chemotherapy including an anthracycline and a taxane are likely to receive a combination of eribulin mesilate and [redacted] or [redacted].

The assumed pharmacokinetic drug interaction between eribulin and [redacted] or [redacted] in the mentioned patient population is unlikely to cause concern. Nevertheless, no relevant data are available from clinical studies, and the optimal dosing regimen of each drug to be combined is unknown. At present, therefore, eribulin mesilate is most recommended to be used alone.

As of October 2010, a clinical study to examine the clinical benefits of eribulin mesilate in combination with [redacted] is being planned.

PMDA's view on the use of eribulin mesilate in combination with other antitumor drugs:

The use of eribulin mesilate with other antitumor drugs including [redacted] and [redacted] is not recommended at present because of the lack of efficacy and safety data on the combination therapy. The "Precautions for Dosage and Administration" section of package insert should highlight that the efficacy and safety of eribulin mesilate in combination with other antitumor drugs have not been established.

4.(iii).B.(6) Post-marketing investigations

The applicant's explanation on the post-marketing surveillance plan:

The applicant plans to conduct post-marketing surveillance covering all patients with inoperable or recurrent breast cancer who receive eribulin mesilate in routine clinical practice. The survey will collect data on (a) unknown adverse drug reactions, (b) the incidence and severity of adverse drug reactions, and (c) factors that may affect the efficacy and safety of eribulin mesilate.

Bone marrow depression (e.g., neutropenia, leukopenia) and serious infections will be selected as key survey items because bone marrow depression occurred frequently in Japanese Study E7389-J081-221.

The target sample size of the survey was determined to be 500 with a focus on infrequent serious infections listed as key survey items. In the foreign studies, the incidences of sepsis and pneumonia were

0.6% and 0.5%, respectively. The proposed target sample size is 500 because it exceeds 460, a sample size that has 90% power to detect an adverse drug reaction with the incidence of 0.5% from ≥1 patient. The surveillance is planned to be performed at approximately 500 institutions (e.g., departments of breast medicine, mammary gland surgery, and oncology), the top [redacted]% of [redacted]. The enrollment period is planned to be 6 months.

The observation period was determined to be 1 year. In Japanese Study E7389-J081-221, eribulin mesilate was administered for the median treatment cycles of 5 (median exposure time, 104.5 days), and only 1 of 81 subjects (1.2%) received eribulin mesilate for ≥1 year (approximately ≥17.5 cycles). Therefore, a period of 1 year should allow observation of all subjects throughout their treatment period.

The final analysis will be performed on data obtained from 500 patients treated with eribulin mesilate by the end of the 1-year observation period (probably 2 years and 6 months after the start of the survey). Interim analyses will be performed 1 year and 2 years after the start of the survey. The analyses aim to obtain significant safety profiles of eribulin mesilate at the earliest time possible after market release and to provide relevant findings to healthcare professionals. The 1-year interim analysis will involve 100 patients and the 2-year interim analysis 500 patients. Both analyses include only patients who have received up to 5 cycles of treatment.

PMDA's view on the post-marketing surveillance plan proposed by the applicant:
The adverse events that require special attention during eribulin mesilate therapy are bone marrow depression, peripheral nerve disorder, infections, hepatic function disorder, and interstitial lung disease. These are known adverse events of other tubulin-targeting drugs as well, and there are no other adverse events specific to eribulin mesilate requiring attention. However, the submitted data provide limited safety data from Japanese patients (a total of 96 Japanese patients; 15 and 81 in Japanese Studies E7389-J081-105 and E7389-J081-221, respectively), and thus limited safety information is available. The applicant should collect further safety data via post-marketing surveillance.

The proposed key survey items, namely infections and bone marrow depression, are appropriate. The survey plan should be reviewed to ensure that data on peripheral nerve disorder, hepatic function disorder, and interstitial lung disease are collected through the survey.

The proposed sample size and observation period are acceptable.

PMDA will draw final conclusions on the survey method in light of comments made in the Expert Discussion.

4.(iv).A Adverse events and other relevant findings observed in clinical studies

The following subsections summarize major non-fatal adverse events in the clinical study results included in the safety evaluation data. Deaths are summarized in "4.(iii) Summary of clinical efficacy and safety."

4.(iv).A.(1) Japanese phase I study (Japanese Study E7389-J081-105)

Adverse events occurred in 15 of 15 subjects (100%) receiving eribulin mesilate, and a causal relationship of the event with the study drug could not be ruled out in 15 of 15 subjects (100%). According to an analysis by treatment group, adverse events occurred in 3 of 3 subjects (100%) in the 0.7 mg/m^2 group, 3 of 3 subjects (100%) in the 1.0 mg/m^2 group, 6 of 6 subjects (100%) in the 1.4 mg/m^2 group, and 3 of 3 subjects (100%) in the 2.0 mg/m^2 group, and the same was true for the adverse events for which a causal relationship with the study drug could not be ruled out. The adverse events with an incidence of ≥20% in all treatment groups combined are shown in the table below.

Adverse events with an incidence of ≥20% in all treatment groups combined (number of subjects; %)

System Organ Class	0.7 mg/m^2 (n = 3)		1.0 mg/m^2 (n = 3)		1.4 mg/m^2 (n = 6)	
Preferred Term	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	3 (100)	2 (66.7)	3 (100)	2 (66.7)	6 (100)	6 (100)
Blood and lymphatic system disorders						
Febrile neutropenia	0	0	0	0	3 (50)	3 (50)
Gastrointestinal disorders						
Constipation	2 (66.7)	0	1 (33.3)	0	1 (16.7)	0
Nausea	2 (66.7)	0	2 (66.7)	0	3 (50)	0
Stomatitis	0	0	0	0	0	0
Vomiting	3 (100)	0	0	0	1 (16.7)	0
General disorders and administration site conditions						
Fatigue	3 (100)	0	1 (33.3)	0	3 (50)	1 (16.7)
Oedema	0	0	1 (33.3)	0	1 (16.7)	0
Pyrexia	2 (66.7)	0	0	0	2 (33.3)	0
Investigations						
ALT increased	1 (33.3)	0	2 (66.7)	0	2 (33.3)	0
AST increased	1 (33.3)	0	2 (66.7)	0	4 (66.7)	0
Blood albumin decreased	0	0	0	0	3 (50)	0
Blood creatine phosphokinase increased	0	0	1 (33.3)	0	1 (16.7)	0
Blood glucose increased	1 (33.3)	0	2 (66.7)	0	6 (100)	0
Blood lactate dehydrogenase increased	0	0	0	0	0	0
Blood sodium decreased	2 (66.7)	0	0	0	0	0
C-reactive protein increased	3 (100)	0	0	0	5 (83.3)	0
Gamma glutamyl transpeptidase increased	2 (66.7)	0	0	0	2 (33.3)	0
Glucose urine present	0	0	1 (33.3)	0	2 (33.3)	0
Haemoglobin decreased	1 (33.3)	1 (33.3)	1 (33.3)	0	4 (66.7)	0
Lymphocyte count decreased	2 (66.7)	1 (33.3)	3 (100)	0	5 (83.3)	2 (33.3)
Neutrophil count decreased	0	0	3 (100)	1 (33.3)	6 (100)	6 (100)
Platelet count decreased	0	0	1 (33.3)	0	1 (16.7)	0
Red blood cell count decreased	1 (33.3)	1 (33.3)	1 (33.3)	0	5 (83.3)	0
White blood cell count decreased	1 (33.3)	0	3 (100)	1 (33.3)	6 (100)	6 (100)
Protein urine present	1 (33.3)	0	1 (33.3)	0	1 (16.7)	0
Blood alkaline phosphatase increased	1 (33.3)	0	0	0	1 (16.7)	0
Metabolism and nutrition disorders						
Decreased appetite	2 (66.7)	0	1 (33.3)	0	3 (50)	0
Nervous system disorders						
Neuropathy peripheral	0	0	0	0	2 (33.3)	1 (16.7)
Respiratory, thoracic and mediastinal disorders						
Cough	1 (33.3)	0	0	0	1 (16.7)	0

System Organ Class Preferred Term	0.7 mg/m^2 (n = 3)		1.0 mg/m^2 (n = 3)		1.4 mg/m^2 (n = 6)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Skin and subcutaneous tissue disorders						
Alopecia	0	–	2 (66.7)	–	5 (83.3)	–
Rash	1 (33.3)	0	1 (33.3)	0	1 (16.7)	0

Adverse events with an incidence of ≥20% in all treatment groups combined (number of subjects; %) (continued)

System Organ Class Preferred Term	2.0 mg/m^2 (n = 3)		All (n = 15)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	3 (100)	3 (100)	15 (100)	13 (86.7)
Blood and lymphatic system disorders				
Febrile neutropenia	2 (66.7)	2 (66.7)	5 (33.3)	5 (33.3)
Gastrointestinal disorders				
Constipation	1 (33.3)	0	5 (33.3)	0
Nausea	2 (66.7)	0	9 (60)	0
Stomatitis	3 (100)	0	3 (20)	0
Vomiting	1 (33.3)	0	5 (33.3)	0
General disorders and administration site conditions				
Fatigue	2 (66.7)	1 (33.3)	9 (60)	2 (13.3)
Oedema	1 (33.3)	0	3 (20)	0
Pyrexia	1 (33.3)	0	5 (33.3)	0
Investigations				
ALT increased	1 (33.3)	0	6 (40)	0
AST increased	2 (66.7)	0	9 (60)	0
Blood albumin decreased	2 (66.7)	0	5 (33.3)	0
Blood creatine phosphokinase increased	2 (66.7)	0	4 (26.7)	0
Blood glucose increased	3 (100)	0	12 (80)	0
Blood lactate dehydrogenase increased	3 (100)	0	3 (20)	0
Blood sodium decreased	1 (33.3)	0	3 (20)	0
C-reactive protein increased	2 (66.7)	0	10 (66.7)	0
Gamma glutamyl transpeptidase increased	1 (33.3)	1 (33.3)	5 (33.3)	1 (6.7)
Glucose urine present	0	0	3 (20)	0
Haemoglobin decreased	3 (100)	0	9 (60)	1 (6.7)
Lymphocyte count decreased	3 (100)	0	13 (86.7)	3 (20)
Neutrophil count decreased	3 (100)	3 (100)	12 (80)	10 (66.7)
Platelet count decreased	3 (100)	0	5 (33.3)	0
Red blood cell count decreased	2 (66.7)	0	9 (60)	1 (6.7)
White blood cell count decreased	3 (100)	3 (100)	13 (86.7)	10 (66.7)
Protein urine present	1 (33.3)	0	4 (26.7)	0
Blood alkaline phosphatase increased	1 (33.3)	0	3 (20)	0
Metabolism and nutrition disorders				
Decreased appetite	3 (100)	1 (33.3)	9 (60)	1 (6.7)
Nervous system disorders				
Neuropathy peripheral	2 (66.7)	0	4 (26.7)	1 (6.7)
Respiratory, thoracic, and mediastinal disorders				
Cough	1 (33.3)	0	3 (20)	0
Skin and subcutaneous tissue disorders				
Alopecia	1 (33.3)	–	8 (53.3)	–
Rash	1 (33.3)	0	4 (26.7)	0

Serious adverse events occurred in 5 subjects (33.3%): 1 subject (33.3%) in the 0.7 mg/m^2 group (vomiting), 1 subject (33.3%) in the 1.0 mg/m^2 group (myelodysplastic syndrome), 2 subjects (33.3%) in the 1.4 mg/m^2 group (febrile neutropenia in one subject and nausea and abdominal pain in the other subject), and 1 subject (33.3%) in the 2.0 mg/m^2 group (febrile neutropenia). A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia in 2 subjects and myelodysplastic

syndrome in 1 subject. The serious adverse event occurred by the end of observation period was febrile neutropenia in 2 subjects. Serious adverse events in the other 3 subjects occurred after the completion of the observation period.

Adverse events leading to the discontinuation of eribulin mesilate occurred in 2 subjects (13.3%): platelet count decreased in 1 subject (33.3%) each in the 1.0 and 2.0 mg/m^2 groups. A causal relationship with eribulin mesilate could not be ruled out for the events.

4.(iv).A.(2) Japanese phase II study (Japanese Study E7389-J081-221)

Adverse events occurred in 81 of 81 subjects (100%) receiving eribulin mesilate. The adverse events with an incidence of ≥10% are shown in the table below. The 81 subjects (100%) also experienced adverse events for which a causal relationship with the study drug could not be ruled out.

Adverse events with an incidence of ≥10% (number of subjects; %)

System Organ Class Preferred Term	(n = 81) All grades	 Grade 3 or 4
All adverse events	81 (100)	78 (96.3)
Blood and lymphatic system disorders		
Febrile neutropenia	11 (13.6)	11 (13.6)
Leukopenia	80 (98.8)	60 (74.1)
Lymphopenia	44 (54.3)	10 (12.3)
Neutropenia	80 (98.8)	77 (95.1)
Gastrointestinal disorders		
Constipation	13 (16)	0
Diarrhoea	15 (18.5)	0
Nausea	36 (44.4)	1 (1.2)
Stomatitis	32 (39.5)	2 (2.5)
Vomiting	16 (19.8)	1 (1.2)
General disorders and administration site conditions		
Fatigue	37 (45.7)	1 (1.2)
Malaise	11 (13.6)	2 (2.5)
Pain	9 (11.1)	2 (2.5)
Pyrexia	25 (30.9)	0 0
Infections and infestations		
Nasopharyngitis	21 (25.9)	0
Investigations		
ALT increased	27 (33.3)	3 (3.7)
AST increased	30 (37)	6 (7.4)
Blood albumin decreased	10 (12.3)	1 (1.2)
Blood creatine phosphokinase increased	23 (28.4)	1 (1.2)
Blood glucose increased	12 (14.8)	0
Blood lactate dehydrogenase increased	16 (19.8)	1 (1.2)
C-reactive protein increased	14 (17.3)	0
Gamma glutamyl transpeptidase increased	22 (27.2)	10 (12.3)
Haemoglobin decreased	28 (34.6)	5 (6.2)
Weight decreased	9 (11.1)	0
Blood alkaline phosphatase increased	17 (21)	3 (3.7)
Metabolism and nutrition disorders		
Decreased appetite	38 (46.9)	1 (1.2)
Musculoskeletal and connective tissue disorders		
Arthralgia	14 (17.3)	0
Nervous system disorders		
Dizziness	9 (11.1)	0
Dysgeusia	27 (33.3)	0
Headache	13 (16)	0
Peripheral sensory neuropathy	19 (23.5)	3 (3.7)

System Organ Class Preferred Term	(n = 81) All grades	 Grade 3 or 4
Respiratory, thoracic, and mediastinal disorders		
Cough	13 (16)	1 (1.2)
Skin and subcutaneous tissue disorders		
Alopecia	47 (58)	–
Rash	11 (13.6)	0

Serious adverse events occurred in 13 subjects (16.0%), and a causal relationship with the study drug could not be ruled out for those observed in 8 subjects (9.9%). The reported serious adverse events were stomatitis, infection, and decreased appetite in 2 subjects (2.5%) each, and neutropenia, ascites, gastritis haemorrhagic, nausea, malaise, oedema, pain, pyrexia, upper limb fracture, dehydration, hypercalcaemia, cancer pain, dyspnea, interstitial lung disease, and haemorrhage in 1 subject (1.2%) each. A causal relationship with eribulin mesilate could not be ruled out for stomatitis, infection, and decreased appetite in 2 subjects (2.5%) each and neutropenia, gastritis haemorrhagic, nausea, oedema, pyrexia, and interstitial lung disease in 1 subject (1.2%) each.

Adverse events leading to the discontinuation of eribulin mesilate occurred in 6 subjects (7.4%), and a causal relationship with eribulin mesilate could not be ruled out for those in 5 subjects (6.2%). The adverse events leading to the discontinuation of eribulin mesilate were neutropenia, stomatitis, fatigue, ALT increased, decreased appetite, cancer pain, dysgeusia, peripheral sensory neuropathy, and interstitial lung disease in 1 subject (1.2%) each. A causal relationship with eribulin mesilate could not be ruled out for neutropenia, stomatitis, fatigue, ALT increased, decreased appetite, dysgeusia, peripheral sensory neuropathy, and interstitial lung disease in 1 subject (1.2%) each.

4.(iv).A.(3) Foreign phase I study (Foreign Study E7389-A001-101)

Adverse events occurred in 32 of 32 subjects (100%) receiving eribulin mesilate, and a causal relationship with the study drug could not be ruled out for the events observed in 28 subjects (87.5%). The adverse events occurred in 2 of 2 subjects (100%) in the 0.25 mg/m^2 group, 8 of 8 subjects (100%) in the 0.5 mg/m^2 group, 4 of 4 subjects (100%) in the 0.7 mg/m^2 group, 9 of 9 subjects (100%) in the 1.0 mg/m^2 group, and 9 of 9 subjects (100%) in the 1.4 mg/m^2 group. A causal relationship with the study drug could not be ruled out for adverse events occurring in 2 of 2 subjects (100%) in the 0.25 mg/m^2 group, 6 of 8 subjects (75.0%) in the 0.5 mg/m^2 group, 4 of 4 subjects (100%) in the 0.7 mg/m^2 group, 7 of 9 subjects (77.8%) in the 1.0 mg/m^2 group, and 9 of 9 subjects (100%) in the 1.4 mg/m^2 group. The adverse events with an incidence of ≥20% in all treatment groups combined are shown in the table below.

Adverse events with an incidence of ≥20% in all treatment groups combined (number of subjects; %)

System Organ Class Preferred Term	0.25 mg/m^2 (n = 2)		0.5 mg/m^2 (n = 8)		0.7 mg/m^2 (n = 4)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	2 (100)	0	8 (100)	3 (37.5)	4 (100)	3 (75)
Blood and lymphatic system disorders						
Neutropenia	0	0	1 (12.5)	1 (12.5)	0	0
Gastrointestinal disorders						
Constipation	0	0	2 (25)	0	0	0
Diarrhoea	1 (50)	0	0	0	0	0
Nausea	1 (50)	0	2 (25)	0	2 (50)	0
Vomiting	2 (100)	0	0 0	0	1 (25)	0
General disorders and administration site conditions						
Fatigue	0	0	4 (50)	1 (12.5)	3 (75)	2 (50)
Metabolism and nutrition disorders						
Decreased appetite	0	0	1 (12.5)	0	2 (50)	0
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (50)	0	2 (25)	0	2 (50)	0

Adverse events with an incidence of ≥20% in all treatment groups combined (number of subjects; %) (continued)

System Organ Class Preferred Term	1.0 mg/m^2 (n = 9)		1.4 mg/m^2 (n = 9)		All (n = 32)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	9 (100)	7 (77.8)	9 (100)	6 (66.7)	32 (100)	19 (59.4)
Blood and lymphatic system disorders						
Neutropenia	2 (22.2)	0	6 (66.7)	6 (66.7)	9 (28.1)	7 (21.9)
Gastrointestinal disorders						
Constipation	3 (33.3)	1 (11.1)	3 (33.3)	0	8 (25)	1 (3.1)
Diarrhoea	4 (44.4)	0	5 (55.6)	0	10 (31.3)	0
Nausea	4 (44.4)	0	5 (55.6)	0	14 (43.8)	0
Vomiting	2 (22.2)	1 (11.1)	3 (33.3)	0	8 (25)	1 (3.1)
General disorders and administration site conditions						
Fatigue	6 (66.7)	1 (11.1)	6 (66.7)	1 (11.1)	19 (59.4)	5 (15.6)
Metabolism and nutrition disorders						
Decreased appetite	5 (55.6)	1 (11.1)	7 (77.8)	0	15 (46.9)	1 (3.1)
Respiratory, thoracic, and mediastinal disorders						
Cough	2 (22.2)	0	1 (11.1)	0	8 (25)	0

Serious adverse events occurred in 12 subjects (37.5%): 0 subjects (0%) in the 0.25 mg/m^2 group, 2 subjects (25.0%) in the 0.5 mg/m^2 group, 2 subjects (50.0%) in the 0.7 mg/m^2 group, 4 subjects (44.4%) in the 1.0 mg/m^2 group, and 4 subjects (44.4%) in the 1.4 mg/m^2 group. In the 0.5 mg/m^2 group, *Klebsiella* bacteraemia, pulmonary embolism, renal failure, pain, and ascites occurred in 1 subject (12.5%) each. A causal relationship with eribulin mesilate was ruled out for all events. In the 0.7 mg/m^2 group, chest pain, fatigue, paraparesis, and spinal cord compression occurred in 1 subject (25.0%) each, and a causal relationship with eribulin mesilate was ruled out for all events. In the 1.0 mg/m^2 group, ascites was observed in 2 subjects (22.2%) and hypoxia, brain injury, multi-organ failure, sepsis, pleural effusion, vomiting, and nausea occurred in 1 subject (11.1%) each. A causal relationship with eribulin mesilate could not be ruled out for hypoxia, brain injury, and vomiting in 1 subject (11.1%) each. In the 1.4 mg/m^2 group, hypoxia, febrile neutropenia, anaemia, catheter related infection, chest pain, dyspnea, and small intestinal obstruction occurred in 1 subject (11.1%) each. A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia, anaemia, and catheter related infection in 1 subject (11.1%) each.

Adverse events leading to the discontinuation of eribulin mesilate occurred in 3 subjects (9.4%): 1 subject (25.0%) in the 0.7 mg/m^2 group (chest pain), 1 subject (11.1%) in the 1.0 mg/m^2 group (sepsis), and 1 subject (11.1%) in the 1.4 mg/m^2 group (hypoxia). A causal relationship with eribulin mesilate was ruled out for all events.

4.(iv).A.(4) Foreign phase I study (Foreign Study E7389-A001-102)

Adverse events occurred in 20 of 21 subjects (95.2%) receiving eribulin mesilate, and a causal relationship with the study drug could not be ruled out for events in 18 subjects (85.7%). The adverse events occurred in 1 of 1 subject (100%) in the 0.25 mg/m^2 group, 4 of 4 subjects (100%) in the 0.5 mg/m^2 group, 2 of 3 subjects (66.7%) in the 1.0 mg/m^2 group, 7 of 7 subjects (100%) in the 2.0 mg/m^2 group, 3 of 3 subjects (100%) in the 2.8 mg/m^2 group, and 3 of 3 subjects (100%) in the 4.0 mg/m^2 group. A causal relationship between the event and the study drug could not be ruled out in 0 of 1 subject (0%) in the 0.25 mg/m^2 group, 4 of 4 subjects (100%) in the 0.5 mg/m^2 group, 2 of 3 subjects (66.7%) in the 1.0 mg/m^2 group, 6 of 7 subjects (85.7%) in the 2.0 mg/m^2 group, 3 of 3 subjects (100%) in the 2.8 mg/m^2 group, and 3 of 3 subjects (100%) in the 4.0 mg/m^2 group. The adverse events that occurred at an incidence of ≥20% in all treatment groups combined are shown in the table below.

Adverse events with an incidence of ≥20% in all treatment groups combined (number of subjects; %)

System Organ Class	0.25 mg/m^2 (n = 1)		0.5 mg/m^2 (n = 4)		1.0 mg/m^2 (n = 3)	
Preferred Term	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	1 (100)	0	4 (100)	2 (50)	2 (66.7)	2 (66.7)
Blood and lymphatic system disorders						
Anaemia	0	0	1 (25)	0	1 (33.3)	0
Febrile neutropenia	0	0	0	0	0	0
Neutropenia	0	0	0	0	1 (33.3)	1 (33.3)
Gastrointestinal disorders						
Constipation	0	0	2 (50)	1 (25)	0	0
Nausea	0	0	2 (50)	0	1 (33.3)	0
General disorders and administration site conditions						
Fatigue	0	0	2 (50)	0	2 (66.7)	0
Metabolism and nutrition disorders						
Decreased appetite	0	0	2 (50)	0	1 (33.3)	0
Musculoskeletal and connective tissue disorders						
Back pain	0	0	0	0	2 (66.7)	1 (33.3)
Skin and subcutaneous tissue disorders						
Alopecia	0	–	0	–	0	–

Adverse events with an incidence of ≥20% (number of subjects; %) (continued)

System Organ Class Preferred Term	2.0 mg/m^2 (n = 7)		2.8 mg/m^2 (n = 3)		4.0 mg/m^2 (n = 3)		All (n = 21)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	7 (100)	6 (85.7)	3 (100)	3 (100)	3 (100)	3 (100)	20 (95.2)	16 (76.2)
Blood and lymphatic system disorders								
Anaemia	2 (28.6)	0	1 (33.3)	0	1 (33.3)	0	6 (28.6)	0
Febrile neutropenia	1 (14.3)	1 (14.3)	2 (66.7)	2 (66.7)	3 (100)	3 (100)	6 (28.6)	6 (28.6)
Neutropenia	5 (71.4)	4 (57.1)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	8 (38.1)	7 (33.3)
Gastrointestinal disorders								
Constipation	2 (28.6)	0	0	0	2 (66.7)	0	6 (28.6)	1 (4.8)
Nausea	0	0	0	0	2 (66.7)	0	5 (23.8)	0
General disorders and administration site conditions								
Fatigue	4 (57.1)	1 (14.3)	2 (66.7)	0	1 (33.3)	0	11 (52.4)	1 (4.8)
Metabolism and nutrition disorders								
Decreased appetite	3 (42.9)	0	1 (33.3)	0	0	0	7 (33.3)	0
Musculoskeletal and connective tissue disorders								
Back pain	3 (42.9)	0	0	0	0	0	5 (23.8)	1 (4.8)
Skin and subcutaneous tissue disorders								
Alopecia	3 (42.9)	–	1 (33.3)	–	3 (100)	–	7 (33.3)	–

Serious adverse events occurred in 10 subjects (47.6%): 0 subjects in the 0.25 mg/m^2 group, 1 subject (25.0%) in the 0.5 mg/m^2 group, 1 subject (33.3%) in the 1.0 mg/m^2 group, 3 subjects (42.9%) in the 2.0 mg/m^2 group, 2 subjects (66.7%) in the 2.8 mg/m^2 group, and 3 subjects (100%) in the 4.0 mg/m^2 group. In the 0.5 mg/m^2 group, ileus occurred in 1 subject (25.0%), which was assessed as not related to eribulin mesilate. In the 1.0 mg/m^2 group, diarrhoea, hyponatraemia, and myocardial infarction occurred in 1 subject (33.3%) each, and a causal relationship to eribulin mesilate could not be ruled out for hyponatremia. In the 2.0 mg/m^2 group, febrile neutropenia, pyrexia, infection, metastases to the central nervous system, pleural effusion, headache, fatigue, and pneumonia occurred in 1 subject (14.3%) each. A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia, pyrexia, and infection. In the 2.8 mg/m^2 group, febrile neutropenia occurred in 2 subjects (66.7%) and cellulitis and bacteraemia occurred in 1 subject (33.3%) each. A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia in 2 subjects. In the 4.0 mg/m^2 group, febrile neutropenia occurred in 3 subjects (100%) and dysphagia and metastases to the central nervous system occurred in 1 subject (33.3%) each. A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia in 3 subjects.

Adverse events leading to the discontinuation of eribulin mesilate occurred in 3 subjects (14.3%): 1 subject (14.3%) in the 2.0 mg/m^2 group (pneumonia), 1 subject (33.3%) in the 2.8 mg/m^2 group (bacteraemia), and 1 subject (33.3%) in the 4.0 mg/m^2 group (metastases to the central nervous system). All these adverse events were assessed as not related to eribulin mesilate.

4.(iv).A.(5) Foreign phase I study (Foreign Study E7389-E044-103)

Adverse events occurred in 4 of 6 subjects (66.7%) receiving eribulin mesilate, and a causal relationship with the study drug could not be ruled out for the events in 4 subjects (66.7%). The adverse events that occurred at an incidence of ≥20% are shown in the table below.

Adverse events with an incidence of ≥20% (number of subjects; %)

System Organ Class Preferred Term	(n = 6)	
	All grades	Grade 3 or 4
All adverse events	4 (66.7)	1 (16.7)
General disorders and administration site conditions		
Fatigue	4 (66.7)	0
Nervous system disorders		
Headache	2 (33.3)	0
Respiratory, thoracic, and mediastinal disorders		
Dyspnoea	2 (33.3)	1 (16.7)

Neither serious adverse events nor adverse events leading to the discontinuation of eribulin mesilate occurred in the study.

4.(iv).A.(6) Foreign phase I study (Foreign Study E7389-E044-108)

Adverse events occurred in 17 of 17 subjects (100%) receiving eribulin mesilate, and a causal relationship with the study drug could not be ruled out for the events in 13 subjects (76.5%). According to an analysis by treatment group, adverse events occurred in 6 of 6 subjects (100%) with normal hepatic function, 7 of 7 subjects (100%) with mild hepatic impairment, and 4 of 4 subjects (100%) with moderate hepatic impairment. A causal relationship with the study drug could not be ruled out for adverse events observed in 4 of 6 subjects (66.7%) with normal hepatic function, 6 of 7 subjects (85.7%) with mild hepatic impairment, and 3 of 4 subjects (75.0%) with moderate hepatic impairment. The table below shows adverse events occurring with an incidence of ≥20% in all treatment groups combined.

Adverse events with an incidence of ≥20% in all treatment groups combined (number of subjects; %)

System Organ Class Preferred Term	Normal hepatic function (n = 6)		Mild hepatic impairment (n = 7)		Moderate hepatic impairment (n = 4)		All (n = 17)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	6 (100)	0	7 (100)	2 (28.6)	4 (100)	2 (50)	17 (100)	4 (23.5)
Gastrointestinal disorders								
Constipation	2 (33.3)	0	2 (28.6)	0	0	0	4 (23.5)	0
Diarrhoea	1 (16.7)	0	2 (28.6)	0	1 (25)	0	4 (23.5)	0
Nausea	3 (50)	0	4 (57.1)	0	1 (25)	1 (25)	8 (47.1)	1 (5.9)
Vomiting	0	0	3 (42.9)	0	2 (50)	1 (25)	5 (29.4)	1 (5.9)
General disorders and administration site conditions								
Fatigue	1 (16.7)	0	3 (42.9)	1 (14.3)	1 (25)	0	5 (29.4)	1 (5.9)
Skin and subcutaneous tissue disorders								
Alopecia	2 (33.3)	–	3 (42.9)	–	2 (50)	–	7 (41.2)	–

Serious adverse events occurred in 2 subjects (11.8%): 0 subjects with normal hepatic function, 1 subject (14.3%) with mild hepatic impairment, and 1 subject (25.0%) with moderate hepatic impairment. The serious adverse events reported in 1 subject with mild hepatic impairment were rib fracture and pleural

effusion, and that reported in 1 subject with moderate hepatic impairment was duodenal obstruction. A causal relationship with eribulin mesilate was ruled out for all events.

There were no adverse events leading to the discontinuation of eribulin mesilate.

4.(iv).A.(7) Foreign phase I study (Foreign Study E7389-E044-109)

Adverse events occurred in 12 of 12 subjects (100%) receiving eribulin mesilate, and a causal relationship with the study drug could not be ruled out for the adverse events observed in all 12 subjects (100%). Adverse events occurred in 12 of 12 subjects (100%) in the monotherapy phase and 7 of 10 subjects (70.0%) in the combination therapy phase. A causal relationship with the study drug could not be ruled out for the events observed in 10 of 12 subjects (83.3%) in the monotherapy phase and 6 of 10 subjects (60.0%) in the combination therapy phase. The adverse events that occurred at an incidence of ≥20% are shown in the table below.

Adverse events with an incidence of ≥20% (number of subjects; %)

System Organ Class	Monotherapy phase (n = 12)		Combination therapy phase (n = 10)		Main evaluation period (n = 12)	
Preferred Term	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	12 (100)	6 (50)	7 (70)	1 (10)	12 (100)	6 (50)
Gastrointestinal disorders						
Nausea	4 (33.3)	0	3 (30)	0	6 (50)	0
Vomiting	3 (25)	1 (8.3)	1 (10)	0	4 (33.3)	1 (8.3)
Abdominal pain	2 (16.7)	0	1 (10)	0	3 (25)	0
Constipation	2 (16.7)	0	2 (20)	0	3 (25)	0
Stomatitis	3 (25)	0	0	0	3 (25)	0
General disorders and administration site conditions						
Fatigue	4 (33.3)	1 (8.3)	3 (30)	1 (10)	6 (50)	2 (16.7)
Oedema peripheral	2 (16.7)	0	1 (10)	0	3 (25)	0
Skin and subcutaneous tissue disorders						
Alopecia	3 (25)	–	0	–	3 (25)	–
Blood and lymphatic system disorders						
Neutropenia	4 (33.3)	4 (33.3)	0	0	4 (33.3)	4 (33.3)

Serious adverse events occurred in 2 subjects (16.7%): 1 subject (8.3%; ileus) in the monotherapy phase and 1 subject (10.0%; anaemia) in the combination therapy phase A causal relationship with eribulin mesilate was ruled out for the both events.

Adverse events leading to the discontinuation of eribulin mesilate occurred in 1 subject (8.3%): 1 subject (8.3%) in the monotherapy phase and 0 subjects (0%) in the combination therapy phase. They were ALT increased and AST increased, and a causal relationship with eribulin mesilate could not be ruled out for these events.

4.(iv).A.(8) Foreign phase I study (Foreign Study E7389-E044-110)

Adverse events occurred in 26 of 26 subjects (100%) receiving eribulin mesilate, and a causal relationship with the study drug could not be ruled out for the events in 24 of 26 subjects (92.3%). The adverse events that occurred at an incidence of ≥20% are shown in the table below.

Adverse events with an incidence of ≥20% (number of subjects; %)

System Organ Class Preferred Term	(n = 26)	
	All grades	Grade 3 or 4
All adverse events	26 (100)	20 (76.9)
Blood and lymphatic system disorders		
Anaemia	8 (30.8)	2 (7.7)
Leukopenia	8 (30.8)	5 (19.2)
Neutropenia	13 (50)	11 (42.3)
Gastrointestinal disorders		
Constipation	9 (34.6)	0
Nausea	8 (30.8)	1 (3.8)
Vomiting	9 (34.6)	2 (7.7)
General disorders and administration site conditions		
Asthenia	11 (42.3)	2 (7.7)
Pyrexia	7 (26.9)	0
Metabolism and nutrition disorders		
Decreased appetite	6 (23.1)	1 (3.8)
Skin and subcutaneous tissue disorders		
Alopecia	6 (23.1)	–

The following serious adverse events occurred in 7 subjects (26.9%): urinary retention, bone pain, headache, vomiting, subileus, bacteraemia, anaemia, asthenia, decreased appetite, renal failure, pyrexia, and hepatitis in 1 subject (3.8%) each. A causal relationship with eribulin mesilate could not be ruled out for anaemia, asthenia, decreased appetite, renal failure, pyrexia, and hepatitis.

An adverse event leading to the discontinuation of eribulin mesilate occurred in 1 subject (3.8%; renal failure). A causal relationship with eribulin mesilate could not be ruled out for the event.

4.(iv).A.(9) Foreign phase II study (Foreign Study E7389-A001-201)

Adverse events occurred in 102 of 103 subjects (99.0%) receiving eribulin mesilate, and a causal relationship with the study drug could not be ruled out for the events in 97 subjects (94.2%). The adverse events occurred in 69 of 70 subjects (98.6%) in the 4-week cycle (once weekly treatment for 3 weeks + 1-week recovery) group and in 33 of 33 subjects (100%) in the 3-week cycle (once weekly treatment for 2 weeks + 1-week recovery) group. A causal relationship with the study drug could not be ruled out for the events in 68 of 70 subjects (97.1%) in the 4-week cycle group and in 29 of 33 subjects (87.9%) in the 3-week cycle group. The adverse events that occurred at an incidence of ≥10% in all treatment cycle groups combined are shown in the table below.

Adverse events with an incidence of ≥10% in all treatment cycle groups combined (number of subjects; %)

System Organ Class Preferred Term	4-week cycle (n = 70)		3-week cycle (n = 33)		All (n = 103)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	69 (98.6)	55 (78.6)	33 (100)	22 (66.7)	102 (99)	77 (74.8)
Blood and lymphatic system disorders						
Anaemia	34 (48.6)	1 (1.4)	7 (21.2)	1 (3)	41 (39.8)	2 (1.9)
Leukopenia	22 (31.4)	14 (20)	6 (18.2)	5 (15.2)	28 (27.2)	19 (18.4)
Neutropenia	54 (77.1)	46 (65.7)	24 (72.7)	20 (60.6)	78 (75.7)	66 (64.1)
Gastrointestinal disorders						
Abdominal pain	9 (12.9)	1 (1.4)	5 (15.2)	3 (9.1)	14 (13.6)	4 (3.9)
Constipation	25 (35.7)	0	10 (30.3)	0	35 (34)	0
Diarrhoea	11 (15.7)	1 (1.4)	8 (24.2)	2 (6.1)	19 (18.4)	3 (2.9)
Dyspepsia	8 (11.4)	0	4 (12.1)	0	12 (11.7)	0
Nausea	32 (45.7)	1 (1.4)	14 (42.4)	2 (6.1)	46 (44.7)	3 (2.9)
Stomatitis	11 (15.7)	3 (4.3)	6 (18.2)	0	17 (16.5)	3 (2.9)
Vomiting	13 (18.6)	0	8 (24.2)	0	21 (20.4)	0
General disorders and administration site conditions						
Fatigue	41 (58.6)	2 (2.9)	19 (57.6)	2 (6.1)	60 (58.3)	4 (3.9)
Oedema peripheral	17 (24.3)	2 (2.9)	5 (15.2)	0	22 (21.4)	2 (1.9)
Pain	8 (11.4)	1 (1.4)	3 (9.1)	2 (6.1)	11 (10.7)	3 (2.9)
Pyrexia	23 (32.9)	2 (2.9)	8 (24.2)	1 (3)	31 (30.1)	3 (2.9)
Infections and infestations						
Urinary tract infection	9 (12.9)	0	5 (15.2)	0	14 (13.6)	0
Investigations						
Weight decreased	10 (14.3)	1 (1.4)	1 (3)	0	11 (10.7)	1 (1)
Metabolism and nutrition disorders						
Dehydration	11 (15.7)	5 (7.1)	3 (9.1)	1 (3)	14 (13.6)	6 (5.8)
Hypokalaemia	12 (17.1)	1 (1.4)	7 (21.2)	2 (6.1)	19 (18.4)	3 (2.9)
Decreased appetite	22 (31.4)	0	9 (27.3)	1 (3)	31 (30.1)	1 (1)
Musculoskeletal and connective tissue disorders						
Arthralgia	10 (14.3)	1 (1.4)	3 (9.1)	0	13 (12.6)	1 (1)
Back pain	7 (10)	0	5 (15.2)	1 (3)	12 (11.7)	1 (1)
Bone pain	10 (14.3)	0	3 (9.1)	0	13 (12.6)	0
Nervous system disorders						
Dizziness	10 (14.3)	0	7 (21.2)	0	17 (16.5)	0
Headache	12 (17.1)	1 (1.4)	11 (33.3)	1 (3)	23 (22.3)	2 (1.9)
Neuropathy peripheral	17 (24.3)	2 (2.9)	9 (27.3)	0	26 (25.2)	2 (1.9)
Respiratory, thoracic and mediastinal disorders						
Cough	16 (22.9)	1 (1.4)	7 (21.2)	1 (3)	23 (22.3)	2 (1.9)
Dyspnoea	15 (21.4)	6 (8.6)	8 (24.2)	3 (9.1)	23 (22.3)	9 (8.7)
Oropharyngeal pain	6 (8.6)	0	6 (18.2)	0	12 (11.7)	0
Skin and subcutaneous tissue disorders						
Alopecia	31 (44.3)	–	14 (42.4)	–	45 (43.7)	–

Serious adverse events occurred in 33 subjects (32.0%): 23 subjects (32.9%) in the 4-week cycle group and 10 subjects (30.3%) in the 3-week cycle group. A causal relationship with the study drug could not be ruled out for serious adverse events in 13 subjects (12.6%): 10 subjects (14.3%) in the 4-week cycle group and 3 subjects (9.1%) in the 3-week cycle group. In the 4-week cycle group, frequent serious adverse events (reported in ≥2 subjects) were dehydration in 5 subjects (7.1%), pyrexia in 3 subjects (4.3%), and febrile neutropenia, malignant neoplasm progression, ataxia, and dyspnea in 2 subjects (2.9%) each. A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia and dehydration in 2 subjects (2.9%) each and neutropenia, thrombocytopenia, inner ear disorder, mucosal inflammation, pyrexia, bronchitis, cellulitis, neutropenic sepsis, pain in an extremity, and ataxia in 1 subject (1.4%) each. In the 3-week cycle group, the following serious adverse events were reported: pain and pyrexia in 2 subjects (6.1%) each and febrile neutropenia, abdominal pain, oesophageal ulcer

haemorrhage, asthenia, hepatic failure, gastroenteritis viral, ankle fracture, dehydration, decreased appetite, malignant neoplasm progression, polyneuropathy, tremor, female genital tract fistula, dyspnea, and pleural effusion in 1 subject (3.0%) each. A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia, pyrexia, and polyneuropathy in 1 subject (3.0%) each.

Adverse events leading to the discontinuation of eribulin mesilate occurred in 13 subjects (12.6%): 11 subjects (15.7%) in the 4-week cycle group and 2 subjects (6.1%) in the 3-week cycle group. A causal relationship with the study drug could not be ruled out for the events in 6 subjects (5.8%): 5 subjects (7.1%) in the 4-week cycle group and 1 subject (3.0%) in the 3-week cycle group. In the 4-week cycle group, the following adverse events lead to the discontinuation of eribulin mesilate: neutropenia, inner ear disorder, diarrhoea, fatigue, disease progression, bacteraemia, meningitis listeria, arthritis bacterial, ataxia, neuropathy peripheral, peripheral sensory neuropathy, respiratory failure, and swelling of the face in 1 subject (1.4%) each. A causal relationship with eribulin mesilate could not be ruled out for neutropenia, inner ear disorder, diarrhoea, fatigue, ataxia, and peripheral sensory neuropathy. In the 3-week cycle group, the following adverse events lead to the discontinuation of eribulin mesilate: pain and polyneuropathy in 1 subject (3.0%) each. A causal relationship with eribulin mesilate could not be ruled out for polyneuropathy.

4.(iv).A.(10) Foreign phase II study (Foreign Study E7389-G000-211)

Adverse events occurred in 290 of 291 subjects (99.7%), and a causal relationship with the study drug could not be ruled out for the events in 287 subjects (98.6%). The adverse events that occurred at an incidence of ≥10% are shown in the table below.

Adverse events with an incidence of ≥10% (number of subjects; %)

System Organ Class Preferred Term	(n = 291) All grades	 Grade 3 or 4
All adverse events	290 (99.7)	214 (73.5)
Blood and lymphatic system disorders		
Anaemia	86 (29.6)	6 (2.1)
Leukopenia	64 (22)	41 (14.1)
Neutropenia	174 (59.8)	157 (54)
Eye disorders		
Lacrimation increased	31 (10.7)	0
Gastrointestinal disorders		
Abdominal pain	38 (13.1)	6 (2.1)
Constipation	95 (32.6)	4 (1.4)
Diarrhoea	65 (22.3)	4 (1.4)
Nausea	141 (48.5)	8 (2.7)
Stomatitis	31 (10.7)	3 (1)
Vomiting	71 (24.4)	6 (2.1)
General disorders and administration site conditions		
Asthenia	111 (38.1)	21 (7.2)
Fatigue	108 (37.1)	12 (4.1)
Mucosal inflammation	44 (15.1)	7 (2.4)
Oedema peripheral	38 (13.1)	2 (0.7)
Pain	32 (11)	8 (2.7)
Pyrexia	85 (29.2)	3 (1)
Infections and infestations		
Urinary tract infection	35 (12)	1 (0.3)
Investigations		
Weight decreased	29 (10)	0
Metabolism and nutrition disorders		
Decreased appetite	84 (28.9)	2 (0.7)
Musculoskeletal and connective tissue disorders		
Arthralgia	50 (17.2)	5 (1.7)
Back pain	46 (15.8)	10 (3.4)
Bone pain	29 (10)	6 (2.1)
Musculoskeletal pain	33 (11.3)	1 (0.3)
Myalgia	42 (14.4)	2 (0.7)
Pain in extremity	38 (13.1)	4 (1.4)
Nervous system disorders		
Dysgeusia	40 (13.7)	0
Headache	61 (21)	3 (1)
Neuropathy peripheral	45 (15.5)	9 (3.1)
Paraesthesia	32 (11)	4 (1.4)
Peripheral sensory neuropathy	30 (10.3)	4 (1.4)
Psychiatric disorders		
Insomnia	33 (11.3)	1 (0.3)
Respiratory, thoracic, and mediastinal disorders		
Cough	57 (19.6)	3 (1)
Dyspnoea	57 (19.6)	13 (4.5)
Skin and subcutaneous tissue disorders		
Alopecia	179 (61.5)	–

Serious adverse events occurred in 88 subjects (30.2%), and a causal relationship with the study drug could not be ruled out for those in 39 subjects (13.4%). Frequent serious adverse events (≥1.0%) were febrile neutropenia in 11 subjects (3.8%), pyrexia in 9 subjects (3.1%), dyspnea in 8 subjects (2.7%), neutropenia and pleural effusion in 7 subjects (2.4%) each, vomiting, pain, and back pain in 4 subjects (1.4%) each, and anaemia, abdominal pain, and metastases to the central nervous system in 3 subjects (1.0%) each. A causal relationship with the study drug could not be ruled out for the following frequent serious events (≥1.0%): febrile neutropenia in 11 subjects (3.8%), neutropenia and pyrexia in 7 subjects (2.4%) each, and anaemia and vomiting in 3 subjects (1.0%) each.

Adverse events leading to the discontinuation of eribulin mesilate occurred in 38 subjects (13.1%), and a causal relationship with eribulin mesilate could not be ruled out for those in 20 subjects (6.9%). Frequent adverse events (≥0.5%) leading to the discontinuation of eribulin mesilate were neuropathy peripheral in 7 subjects (2.4%), and muscular weakness, peripheral motor neuropathy, and peripheral sensory neuropathy in 2 subjects (0.7%) each. A causal relationship with eribulin mesilate could not be ruled out for all events.

4.(iv).A.(11) Foreign phase III study (Foreign Study E7389-G000-305)

In the eribulin mesilate group, adverse events occurred in 497 of 503 subjects (98.8%) and, a causal relationship with eribulin mesilate could not be ruled out for those in 474 subjects (94.2%). In the TPC group, adverse events occurred in 230 of 247 subjects (93.1%), and a causal relationship with TPC could not be ruled out for those in 192 subjects (77.7%). The adverse events that occurred at an incidence of ≥10% are shown in the table below.

Adverse events with an incidence of ≥10% (number of subjects; %)

System Organ Class Preferred Term	Eribulin mesilate (n = 503)		TPC (n = 247)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	497 (98.8)	327 (65)	230 (93.1)	116 (47)
Blood and lymphatic system disorders				
Anaemia	94 (18.7)	10 (2)	56 (22.7)	9 (3.6)
Leukopenia	116 (23.1)	70 (13.9)	28 (11.3)	14 (5.7)
Neutropenia	259 (51.5)	227 (45.1)	73 (29.6)	52 (21.1)
Gastrointestinal disorders				
Constipation	124 (24.7)	4 (0.8)	51 (20.6)	2 (0.8)
Diarrhoea	92 (18.3)	0	45 (18.2)	0
Nausea	174 (34.6)	6 (1.2)	70 (28.3)	7 (2.8)
Vomiting	91 (18.1)	5 (1)	44 (17.8)	3 (1.2)
General disorders and administration site conditions				
Asthenia	133 (26.4)	32 (6.4)	58 (23.5)	13 (5.3)
Fatigue	146 (29)	18 (3.6)	47 (19)	15 (6.1)
Pyrexia	105 (20.9)	1 (0.2)	31 (12.6)	1 (0.4)
Investigations				
Weight decreased	107 (21.3)	4 (0.8)	33 (13.4)	0
Metabolism and nutrition disorders				
Decreased appetite	113 (22.5)	3 (0.6)	36 (14.6)	4 (1.6)
Musculoskeletal and connective tissue disorders				
Arthralgia	70 (13.9)	3 (0.6)	13 (5.3)	2 (0.8)
Back pain	75 (14.9)	4 (0.8)	19 (7.7)	4 (1.6)
Bone pain	56 (11.1)	9 (1.8)	23 (9.3)	5 (2)
Myalgia	53 (10.5)	1 (0.2)	16 (6.5)	1 (0.4)
Pain in extremity	59 (11.7)	5 (1)	24 (9.7)	3 (1.2)
Nervous system disorders				
Headache	97 (19.3)	2 (0.4)	29 (11.7)	1 (0.4)
Neuropathy peripheral	59 (11.7)	16 (3.2)	15 (6.1)	2 (0.8)
Paraesthesia	56 (11.1)	9 (1.8)	16 (6.5)	0
Peripheral sensory neuropathy	63 (12.5)	10 (2)	10 (4)	2 (0.8)
Respiratory, thoracic and mediastinal disorders				
Cough	72 (14.3)	0	21 (8.5)	0
Dyspnoea	79 (15.7)	18 (3.6)	31 (12.6)	8 (3.2)
Skin and subcutaneous tissue disorders				
Alopecia	224 (44.5)	–	24 (9.7)	–
Palmar-plantar erythrodysaesthesia syndrome	7 (1.4)	2 (0.4)	34 (13.8)	9 (3.6)

In the eribulin mesilate group, serious adverse events occurred in 126 subjects (25.0%), and a causal relationship with eribulin mesilate could not be ruled out for those in 59 subjects (11.7%). Frequent serious adverse events (≥1.0%) were febrile neutropenia in 20 subjects (4.0%), neutropenia in 9 subjects (1.8%), nausea, pyrexia, hypercalcaemia, dyspnea, and pulmonary embolism in 7 subjects (1.4%) each, pleural effusion in 6 subjects (1.2%), and vomiting and general physical health deterioration in 5 subjects (1.0%). A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia in 20 subjects (4.0%), neutropenia in 9 subjects (1.8%), and pyrexia in 5 subjects (1.0%).

In the TPC group, serious adverse events occurred in 64 subjects (25.9%), and a causal relationship with TPC could not be ruled out for those in 17 subjects (6.9%). Frequent serious adverse events (≥1.0%) were dyspnea in 9 subjects (3.6%), asthenia in 5 subjects (2.0%), diarrhoea and pleural effusion in 4 subjects (1.6%) each, and febrile neutropenia, abdominal pain, pain, performance status decreased, back pain, malignant neoplasm progression, and pulmonary embolism in 3 subjects (1.2%) each. A causal relationship with TPC could not be ruled out for asthenia in 4 subjects (1.6%) and diarrhoea in 3 subjects (1.2%).

In the eribulin mesilate group, adverse events leading to the discontinuation of treatment occurred in 67 subjects (13.3%), and a causal relationship with eribulin mesilate could not be ruled out for those in 45 subjects (8.9%). Frequent adverse events (≥1.0%) leading to the discontinuation of eribulin mesilate were peripheral sensory neuropathy in 11 subjects (2.2%), neuropathy peripheral in 8 subjects (1.6%), peripheral motor neuropathy in 6 subjects (1.2%), and fatigue in 5 subjects (1.0%). A causal relationship with eribulin mesilate could not be ruled out for peripheral sensory neuropathy in 11 subjects (2.2%), neuropathy peripheral in 7 subjects (1.4%), and peripheral motor neuropathy in 6 subjects (1.2%).

In the TPC group, adverse events leading to the discontinuation of study drug occurred in 38 subjects (15.4%), and a causal relationship with TPC could not be ruled out for those in 17 subjects (6.9%). Frequent adverse events (≥1.0%) leading to the discontinuation of TPC were palmar-plantar erythrodysaesthesia syndrome in 4 subjects (1.6%), and ascites, asthenia, and dyspnea in 3 subjects (1.2%) each. A causal relationship with TPC could not be ruled out for palmar-plantar erythrodysaesthesia syndrome in 4 subjects (1.6%).

4.(iv).A.(12) Foreign phase I study (Foreign Study NCI-5730)

Grade 3 or 4 adverse drug reactions of neutrophil or granulocyte count decreased was reported frequently (14 subjects in Cycle 1; 25 subjects from Cycle 2 onward). The adverse drug reactions reported in ≥2 subjects in Cycle 1, or from Cycle 2 onward are shown in the table below.

Grade 3 or 4 adverse drug reactions reported in ≥2 subjects in Cycle 1, or from Cycle 2 onward (number of subjects)

System organ class Event term	(n = 40)	
	Cycle 1	From Cycle 2 onward
Blood system		
Total white blood cell count decreased	7	5
Neutrophil/granulocyte count decreased	14	25
Febrile neutropenia	2	0
Metabolism		
Hyperglycaemia	1	2

DLT occurred in 0 of 1 subject in the 0.125 mg/m^2 group, 0 of 1 subject in the 0.25 mg/m^2 group, 1 of 7 subjects in the 0.5 mg/m^2 group, 0 of 4 subjects in the 0.7 mg/m^2 group, 0 of 3 subjects in the 1.0 mg/m^2 group, 1 of 19 subjects in the 1.4 mg/m^2 group, and 2 of 5 subjects in the 2.0 mg/m^2 group. They were, namely, febrile neutropenia in 3 subjects and alkaline phosphatase increased in 1 subject. Besides, hyperglycaemia, hypophosphataemia, and fatigue were observed as serious non-hematologic toxicities.

4.(iv).A.(13) Foreign phase II study (Foreign Study E7389-A001-202)

Adverse events occurred in 103 of 103 subjects (100%) receiving eribulin mesilate, and a causal relationship with eribulin mesilate could not be ruled out for those in 95 subjects (92.2%). The events occurred in 77 of 77 subjects (100%) in the 4-week cycle (once weekly treatment for 3 weeks + 1-week recovery) group and 26 of 26 subjects (100%) in the 3-week cycle (once weekly treatment for 2 weeks + 1-week recovery) group. A causal relationship with eribulin mesilate could not be ruled out for those in 70 of 77 subjects (90.9%) in the 4-week cycle group and 25 of 26 subjects (96.2%) in the 3-week cycle group. The adverse events that occurred at an incidence of ≥10% in all treatment cycle groups combined are shown in the table below.

Adverse events with an incidence of ≥10% in all treatment cycle groups combined (number of subjects; %)

System Organ Class Preferred Term	4-week cycle (n = 77)		3-week cycle (n = 26)		All(n = 103)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
All adverse events	77 (100)	54 (70.1)	26 (100)	19 (73.1)	103 (100)	73 (70.9)
Blood and lymphatic system disorders						
Anaemia	27 (35.1)	2 (2.6)	10 (38.5)	2 (7.7)	37 (35.9)	4 (3.9)
Neutropenia	45 (58.4)	38 (49.4)	14 (53.8)	13 (50)	59 (57.3)	51 (49.5)
Gastrointestinal disorders						
Constipation	31 (40.3)	2 (2.6)	15 (57.7)	0	46 (44.7)	2 (1.9)
Diarrhoea	19 (24.7)	3 (3.9)	9 (34.6)	0	28 (27.2)	3 (2.9)
Nausea	38 (49.4)	2 (2.6)	13 (50)	0	51 (49.5)	2 (1.9)
Stomatitis	13 (16.9)	1 (1.3)	1 (3.8)	0	14 (13.6)	1 (1)
Vomiting	24 (31.2)	2 (2.6)	6 (23.1)	1 (3.8)	30 (29.1)	3 (2.9)
General disorders and administration site conditions						
Asthenia	12 (15.6)	4 (5.2)	3 (11.5)	0	15 (14.6)	4 (3.9)
Chest pain	7 (9.1)	3 (3.9)	4 (15.4)	1 (3.8)	11 (10.7)	4 (3.9)
Fatigue	51 (66.2)	15 (19.5)	15 (57.7)	4 (15.4)	66 (64.1)	19 (18.4)
Mucosal inflammation	11 (14.3)	0	2 (7.7)	0	13 (12.6)	0
Oedema peripheral	16 (20.8)	0	7 (26.9)	0	23 (22.3)	0
Pyrexia	24 (31.2)	2 (2.6)	6 (23.1)	0	30 (29.1)	2 (1.9)
Infections and infestations						
Upper respiratory tract infection	10 (13)	0	5 (19.2)	0	15 (14.6)	0
Urinary tract infection	13 (16.9)	0	3 (11.5)	0	16 (15.5)	0
Investigations						
Weight decreased	12 (15.6)	3 (3.9)	2 (7.7)	0	14 (13.6)	3 (2.9)
Breath sounds abnormal	10 (13)	0	2 (7.7)	0	12 (11.7)	0
Metabolism and nutrition disorders						
Dehydration	10 (13)	5 (6.5)	2 (7.7)	0	12 (11.7)	5 (4.9)
Decreased appetite	32 (41.6)	1 (1.3)	13 (50)	0	45 (43.7)	1 (1)
Musculoskeletal and connective tissue disorders						
Arthralgia	18 (23.4)	3 (3.9)	1 (3.8)	0	19 (18.4)	3 (2.9)
Back pain	10 (13)	2 (2.6)	5 (19.2)	1 (3.8)	15 (14.6)	3 (2.9)
Bone pain	10 (13)	6 (7.8)	4 (15.4)	0	14 (13.6)	6 (5.8)
Nervous system disorders						
Dizziness	12 (15.6)	0	7 (26.9)	0	19 (18.4)	0
Neuropathy peripheral	21 (27.3)	2 (2.6)	6 (23.1)	0	27 (26.2)	2 (1. 9)
Peripheral sensory neuropathy	7 (9.1)	1 (1.3)	4 (15.4)	0	11 (10.7)	1 (1)
Psychiatric disorders						
Anxiety	15 (19.5)	3 (3.9)	5 (19.2)	0	20 (19.4)	3 (2.9)
Depression	18 (23.4)	0	3 (11.5)	0	21 (20.4)	0
Insomnia	16 (20.8)	0	4 (15.4)	0	20 (19.4)	0
Respiratory, thoracic, and mediastinal disorders						
Cough	28 (36.4)	2 (2.6)	6 (23.1)	0	34 (33)	2 (1.9)
Dyspnoea	35 (45.5)	14 (18.2)	13 (50)	5 (19.2)	48 (46.6)	19 (18.4)
Wheezing	10 (13)	0	3 (11.5)	0	13 (12.6)	0
Skin and subcutaneous tissue disorders						
Alopecia	34 (44.2)	–	4 (15.4)	–	38 (36.9)	–
Rash	10 (13)	1 (1.3)	2 (7.7)	0	12 (11.7)	1 (1)

Serious adverse events occurred in 44 subjects (42.7%): 33 subjects (42.9%) in the 4-week cycle group and 11 subjects (42.3%) in the 3-week cycle group. A causal relationship with eribulin mesilate could not be ruled out for those in 12 subjects (11.7%): 10 subjects (13.0%) in the 4-week cycle group and 2 subjects (7.7%) in the 3-week cycle group. In the 4-week cycle group, frequent serious adverse events (≥2 subjects) were malignant neoplasm progression in 5 subjects (6.5%), pyrexia, pneumonia, lung neoplasm malignant, dyspnea, and pulmonary embolism in 3 subjects (3.9%) each, and febrile neutropenia, diarrhoea, dehydration, metastases to central nervous system, hypoxia, and respiratory failure in 2 subjects (2.6%) each. A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia in 2 subjects (2.6%) and neutropenia, pancytopenia, gastritis, stomatitis, pyrexia, sepsis, neutropenic sepsis, neuropathy peripheral, dyspnoea, and pulmonary embolism in 1 subject (1.3%). In the 3-week cycle group, the following serious adverse events were reported: deep vein thrombosis in 3 subjects (11.5%), dyspnea and respiratory failure in 2 subjects (7.7%) each, and febrile neutropenia, neutropenia, cardiac tamponade, vomiting, pain, cellulitis, pneumonia, blood pressure systolic inspiratory decreased, ataxia, hypoxia, pleural effusion, pulmonary embolism, and hypotension in 1 subject (3.8%) each. A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia, neutropenia, and pneumonia in 1 subject (3.8%) each.

Adverse events leading to the discontinuation of eribulin mesilate occurred in 15 subjects (14.6%): 13 subjects (16.9%) in the 4-week cycle group and 2 subjects (7.7%) in the 3-week cycle group. A causal relationship with eribulin mesilate could not be ruled out for those in 6 subjects (5.8%): 5 subjects (6.5%) in the 4-week cycle group and 1 subject (3.8%) in the 3-week cycle group. In the 4-week cycle group, the following adverse events led to the discontinuation of eribulin mesilate: fatigue and neuropathy peripheral in 2 subjects (2.6%) each and abdominal pain, asthenia, pneumonia, neutropenic sepsis, collapse of lung, dehydration, bone pain, malignant neoplasm progression, lung neoplasm malignant, metastases to central nervous system, cerebral haemorrhage, haemoptysis, and respiratory failure in 1 subject (1.3%) each. A causal relationship with eribulin mesilate could not be ruled out for fatigue and neuropathy peripheral in 2 subjects (2.6%) each and neutropenic sepsis in 1 subject (1.3%). In the 3-week cycle group, the following adverse events led to the discontinuation of eribulin mesilate: thrombocytopenia, hypoxia, and respiratory failure in 1 subject (3.8%) each. A causal relationship with eribulin mesilate could not be ruled out for thrombocytopenia.

4.(iv).A.(14) Foreign phase II study (Foreign Study E7389-G000-204)

Adverse events occurred in 107 of 108 subjects (99.1%) receiving eribulin mesilate, and a causal relationship with eribulin mesilate could not be ruled out for those in 96 subjects (88.9%). The adverse events that occurred at an incidence of ≥10% are shown in the table below.

Adverse events with an incidence of ≥10% (number of subjects; %)

System Organ Class Preferred Term	(n = 108) All grades	 Grade 3 or 4
All adverse events	107 (99.1)	59 (54.6)
Blood and lymphatic system disorders		
Anaemia	33 (30.6)	4 (3.7)
Leukopenia	28 (25.9)	12 (11.1)
Neutropenia	44 (40.7)	32 (29.6)
Gastrointestinal disorders		
Constipation	24 (22.2)	0
Diarrhoea	26 (24.1)	2 (1.9)
Nausea	25 (23.1)	0
General disorders and administration site conditions		
Asthenia	28 (25.9)	5 (4.6)
Fatigue	47 (43.5)	8 (7.4)
Oedema peripheral	19 (17.6)	2 (1.9)
Pyrexia	16 (14.8)	4 (3.7)
Metabolism and nutrition disorders		
Decreased appetite	27 (25)	0
Musculoskeletal and connective tissue disorders		
Back pain	11 (10.2)	0
Muscular weakness	14 (13)	1 (0.9)
Nervous system disorders		
Neuropathy peripheral	21 (19.4)	3 (2.8)
Paraesthesia	12 (11.1)	3 (2.8)
Skin and subcutaneous tissue disorders		
Alopecia	20 (18.5)	–

Serious adverse events occurred in 34 subjects (31.5%), and a causal relationship with eribulin mesilate could not be ruled out for those in 14 subjects (13.0%). Frequent serious adverse events (≥2 subjects) were pneumonia and renal failure in 4 subjects (3.7%) each, febrile neutropenia, pyrexia, urosepsis, dehydration, spinal cord compression, and pulmonary embolism in 3 subjects (2.8%) each, and anaemia, neutropenia, diarrhoea, melaena, urinary tract infection, malignant neoplasm progression, and deep vein thrombosis in 2 subjects (1.9%) each. A causal relationship with eribulin mesilate could not be ruled out for febrile neutropenia in 3 subjects (2.8%) and neutropenia, diarrhoea, pyrexia, urinary tract infection, pulmonary embolism, and deep vein thrombosis in 2 subjects (1.9%) each.

Adverse events leading to the discontinuation of eribulin mesilate occurred in 27 subjects (25.0%), and a causal relationship with eribulin mesilate could not be ruled out for those in 18 subjects (16.7%). Frequent adverse events (≥2 subjects) leading to the discontinuation of eribulin mesilate were neuropathy peripheral in 6 subjects (5.6%), paraesthesia in 5 subjects (4.6%), spinal cord compression in 3 subjects (2.8%), and asthenia and fatigue in 2 subjects (1.9%) each. A causal relationship with eribulin mesilate could not be ruled out for neuropathy peripheral in 6 subjects (5.6%), paraesthesia in 5 subjects (4.6%), and fatigue in 2 subjects (1.9%).

III. Results of the Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection of the data submitted in the New Drug Application was conducted in accordance with the provisions of the Pharmaceutical Affairs Act. With no particular problems identified, PMDA concluded that there should be no problem in conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of on-site GCP inspection

The inspections are currently underway.

IV. Overall Evaluation

PMDA has concluded that the submitted data demonstrate the efficacy of eribulin mesilate in treating inoperable or recurrent breast cancer and its acceptable safety in view of its observed benefits. Eribulin mesilate contains a new active ingredient that inhibits tubulin polymerization, and is considered to be of clinical value as a new treatment option. PMDA intends to deepen discussion on the indication and dosage and administration of eribulin mesilate and post-marketing investigations at the Expert Discussion.

PMDA considers that eribulin mesilate may be approved if the drug is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

January 11, 2011

I. Product Submitted for Registration

[Brand name] Halaven Injection 1 mg
[Non-proprietary name] Eribulin Mesilate
[Applicant] Eisai Co., Ltd.
[Date of application] March 30, 2010

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions, etc. by the Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

Data from a foreign phase III study (Foreign Study E7389-G000-305) demonstrated the superiority of eribulin mesilate to the treatment of physician's choice (TPC) in the primary endpoint of overall survival (OS). Accordingly, PMDA concluded that eribulin mesilate has efficacy in patients with advanced or recurrent breast cancer previously treated with 2 to 5 chemotherapy regimens including an anthracycline and a taxane.

This conclusion was supported by the expert advisors at the Expert Discussion.

(2) Safety

PMDA's conclusion

In light of the submitted data, the following adverse events require attention during treatment with eribulin mesilate: bone marrow depression, peripheral nerve disorder, infections, hepatic function disorder, and interstitial lung disease. Despite these events, eribulin mesilate is tolerable as long as patients are followed appropriately by a physician with sufficient knowledge and experience in cancer chemotherapy through monitoring and controlling of adverse events and dose adjustment by reduction, suspension, or discontinuation of the drug.

This conclusion was supported by the expert advisors at the Expert Discussion. The following comments were raised by the expert advisors:

- In the ongoing foreign clinical study (Foreign Study E7389-G000-[redacted]), hepatic failure and hepatitis toxic were reported as adverse events resulting in death, and a causal relationship with eribulin mesilate could not be ruled out for the events [see "4.(iii).B.(3).5) Hepatic function disorder" of Review Report (1)]. Detailed clinical courses of these patients should be identified and communicated to healthcare professionals.
- In patients with peripheral nerve disorder caused by prior antineoplastic taxanes or other agents, the dose intensity of eribulin mesilate (total dose received/duration of exposure) may have been reduced because of relapse or worsening of the disorder during treatment. The applicant should investigate whether this led to underestimation of the safety regarding adverse events unrelated to peripheral nerve disorder.
- The Kaplan-Meier curves [see "4.(iii).B.(3).3) Peripheral nerve disorder" of Review Report (1)], although of the small number of subjects, suggest that the cumulative incidence of peripheral nerve disorder and the incidence of higher-grade peripheral nerve disorder may increase with the increasing duration of treatment with eribulin mesilate. Furthermore, patients who have had peripheral nerve disorder before starting treatment may experience more severe peripheral nerve disorder after starting treatment with eribulin mesilate. These facts on peripheral nerve disorder should be appropriately communicated to healthcare professionals through written materials.
- Because limited safety information on eribulin mesilate is available from published literature, etc., the applicant should keep healthcare professionals updated with the latest safety information through written materials.

Some subjects in Foreign Study E7389-G000-[redacted] had hepatic failure or toxic hepatitis with fatal outcome, and a causal relationship with eribulin mesilate could not be ruled out for the events. PMDA asked the applicant to explain the clinical courses of the subjects

The applicant's response:
A subject who had fatal hepatic failure (a woman aged 46 years with metastatic breast cancer to the lung and liver):
The subject experienced serum transaminase increased (AST, 69; ALT, 105 [units unknown]) and Grade 2 serum creatinine increased in Cycle 1 of treatment with eribulin mesilate. The subject died on Day 37. The cause of death may have been the progression of the underlying disease, but a causal relationship between hepatic and renal failure and eribulin mesilate could not be ruled out because no autopsy was performed.

A subject who had fatal toxic hepatitis (a woman aged 52 years with metastatic breast cancer to the lung):
The subject experienced fatigue, weakness, nausea, and vomiting after receiving a dose of eribulin mesilate on Day 1 in Cycle 1. Grade 2 hyperbilirubinaemia and Grade 4 neutrophil count decreased developed on Day 9. Hepatitis toxic was diagnosed. The subject died on Day 14. Because no autopsy

was performed, a causal relationship between hepatitis toxic and eribulin mesilate could not be ruled out.

PMDA's view:
Whether the hepatic failure and toxic hepatitis directly caused the deaths remains unclear. Nevertheless, causal relationships between eribulin mesilate and the events could not be ruled out. The applicant should therefore inform healthcare professionals of the death cases through written materials.

PMDA asked the applicant to explain the relationship between dose intensity and the safety of eribulin mesilate in patients with and without peripheral nerve disorder caused by prior treatment with antitumor drugs.

The applicant's explanation:
The dose intensity of eribulin mesilate was compared by baseline grade of peripheral nerve disorder using the results of a Japanese phase II study (Japanese Study E7389-J081-221) and a pooled analysis of the eribulin mesilate groups in 3 foreign studies (Foreign Studies E7389-A001-201, E7389-G000-211, and E7389-G000-305). The dose intensity did not differ among different grades of baseline peripheral nerve disorder (see the table below).

Dose intensity[*1] by grade of baseline peripheral nerve disorder

Grade of baseline peripheral nerve disorder	Japanese Study E7389-J081-221 (n = 81)		Foreign studies (n = 827)	
	Number of subjects	Dose intensity Median (min, max)	Number of subjects	Dose intensity Median (min, max)
All grades	81	0.760 (0.34, 0.96)	826[*2]	0.860 (0.24, 1.01)
Grade 0	49	0.730 (0.34, 0.96)	624	0.860 (0.24, 0.98)
Grade 1	32	0.785 (0.43, 0.95)	142	0.860 (0.34, 1.01)
Grade ≥2	0	–	27	0.850 (0.41, 0.96)

– not calculated
[*1] Dose intensity = total dose received (mg/m^2)/duration of exposure (weeks)
[*2] Including subjects with unknown baseline grades of peripheral nerve disorder

Similarly, the safety of eribulin mesilate (regarding adverse events of special interest, i.e., Grade 4 neutrophil count decreased, peripheral nerve disorder, asthenia/fatigue, and arthralgia/myalgia) was compared by baseline grade of the peripheral nerve disorder. No differences were detected in the safety profile of eribulin mesilate, including that related to peripheral nerve disorder [see "4.(iii).B.(3).3) Peripheral nerve disorder" of Review Report (1)].

Based on the above results, a baseline peripheral nerve disorder is unlikely to clearly affect the dose intensity or safety of eribulin mesilate.

PMDA accepted the applicant's explanation. However, long-term use of eribulin mesilate may increase the cumulative incidence of peripheral nerve disorder by a certain percentage, and may also increase the incidence of higher-grade peripheral nerve disorder. These risks should be communicated to healthcare professionals. The applicant also should collect more post-marketing data on the possibility that patients

with an existing peripheral nerve disorder may experience more severe peripheral nerve disorder after receiving eribulin mesilate, and communicate new findings to healthcare professionals in an appropriate manner.

Based on the Expert Discussion, PMDA advised the applicant to provide safety information on eribulin mesilate, including that related to peripheral nerve disorder, to healthcare professionals via the package insert or other written materials. The applicant agreed.

(3) Clinical positioning and indication

Clinical benefits of eribulin mesilate have been demonstrated in patients with advanced or recurrent breast cancer who have received 2 to 5 prior chemotherapy regimens including an anthracycline. There are no available standard third-line therapy. Given these, PMDA concluded that eribulin mesilate is a candidate first-line therapeutic option for this patient population.

Furthermore, PMDA concluded that the indication of eribulin mesilate should be defined as "inoperable or recurrent breast cancer" along with the following advice in the "Precautions for Indication" section of the package insert.

- The efficacy and safety of eribulin mesilate for adjuvant or neoadjuvant chemotherapy have not been established.
- Eribulin mesilate is indicated for patients with breast cancer that has worsened or recurred after chemotherapy including an anthracycline and a taxane.

This conclusion was supported by the expert advisors at the Expert Discussion. The following comments were raised by the expert advisors.

- Eribulin mesilate is indicated for patients with breast cancer that has progressed after chemotherapy including an anthracycline and a taxane. The applicant should strive to communicate this to healthcare professionals accurately by working with relevant academic societies as necessary.
- A standard therapy should be established based on data from multiple confirmatory studies and various post-marketing information. It would be rather difficult to regard eribulin mesilate as the first-line therapeutic option for patients with breast cancer previously treated with chemotherapy including an anthracycline and a taxane, based solely on the data from Foreign Study E7389-G000-305.
- Foreign Study [redacted] is being conducted as a comparative study with [redacted]. This clinical study is important because it will help further clarify the clinical position of eribulin mesilate. The applicant should communicate the results of the study to healthcare professionals as soon as available.

Based on the Expert Discussion, PMDA advised the applicant to disseminate information so that healthcare professionals are well-informed of the type of population in which eribulin mesilate was

shown to be safe and effective in the clinical studies. The applicant agreed. In future, eribulin mesilate may be established as a first-line therapeutic option for patients suffering from disease progression after receiving chemotherapy including an anthracycline and a taxane. At present, however, the drug cannot be recognized as a first-line option for the population because of lack of evidence. PMDA advised the applicant to publish the results of Foreign Study [redacted] on their website, etc. as soon as available and communicate them to healthcare professionals. The applicant agreed.

Accordingly, PMDA advised the applicant that the following wording be used for "Indication" and "Precautions for Indication." The applicant agreed.

[Indication]
Inoperable or recurrent breast cancer

[Precautions for Indication]
- The efficacy and safety of eribulin mesilate for adjuvant or neoadjuvant chemotherapy have not been established.
- Eribulin mesilate is indicated for patients with breast cancer that has worsened or recurred after chemotherapy including an anthracycline and a taxane.

(4) Dosage and administration

PMDA's conclusion:

The "Dosage and Administration" section of the package insert should be as follows: "The usual adult dosage is 1.4 mg/m^2 (body surface area) of eribulin mesilate administered intravenously over 2 to 5 minutes at 1 week interval for 2 consecutive weeks, followed by a rest week. This treatment cycle is repeated. The dose may be adjusted according to the patient's condition." The "Precautions for Dosage and Administration" section should include the following:

(a) A note that the efficacy and safety of eribulin mesilate in combination with other antitumor drugs have not been established
(b) Criteria for dose delay, reduction, suspension, and discontinuation
(c) Precautionary advice for the use of eribulin mesilate in patients with hepatic impairment

This conclusion was supported by the expert advisors at the Expert Discussion. The following comments were raised by the expert advisors.

- The proposed infusion time (2 to 5 minutes) cannot be justified from a clinical pharmacology perspective, but some of the reasons for how and why the infusion time was selected are understandable. Therefore, "2 to 5 minutes" (the infusion time evaluated in Foreign Study E7389-G000-305 etc.) is acceptable as the time for infusion of eribulin mesilate.

- It is beneficial to show dose levels of eribulin mesilate specific to patients with hepatic impairment in the package insert, etc., but such dose levels cannot be determined based solely on the results of Foreign Study E7389-E044-108.

Accordingly, PMDA advised the applicant that the following wording be used for the "Dosage and Administration" and "Precautions for Dosage and Administration." The applicant agreed.

[Dosage and Administration]

The usual adult dosage is 1.4 mg/m^2 (body surface area) of eribulin mesilate administered intravenously over 2 to 5 minutes once weekly for 2 consecutive weeks, followed by a rest week. This treatment cycle is repeated. The dose may be adjusted according to the patient's condition.

[Precautions for Dosage and Administration]

- The efficacy and safety of eribulin mesilate in combination with other antitumor drugs have not been established.
- Delay or suspend administration or reduce the dose as needed according to the criteria below.

Recommended dose delays and reductions in Week 1 of each cycle

Start of treatment	Delay the dose if the patient does not meet the following requirements: • Neutrophil count ≥1000/mm^3 • Platelet count ≥75,000/mm^3 • Grade ≤2[Note 1)] non-hematological toxicity
Dose reduction	Use a reduced dose if any of the following has occurred in the previous treatment cycle[Note 2)]: • Neutrophil count decreased (<500/mm^3) lasting for >7 days • Neutrophil count decreased (<1000/mm^3) accompanied by fever or infection • Platelet count decreased (<25,000/mm^3) • Platelet count decreased (<50,000/mm^3) requiring blood transfusion • Grade ≥3[Note 1)] non-hematological toxicity • Suspension of treatment in the second week due to adverse reactions, etc.

Recommended dose delays, reductions, and suspension in Week 2 of each cycle

Start of treatment	Delay the dose if the patient does not meet the following requirements: • Neutrophil count ≥1000/mm^3 • Platelet count ≥75,000/mm^3 • Grade ≤2[Note 1)] non-hematological toxicity
Resumption	Resume the treatment at a reduced dose[Note 2)] if the starting criteria are met within 1 week after treatment delay.
Suspension	Suspend treatment if the starting criteria are not met within 1 week after treatment delay.

[Note 1)] Based on the Common Terminology Criteria for Adverse Events (CTCAE) v. 3.0

[Note 2)] Recommended dose reductions:

Before reduction → After reduction
1.4 mg/m^2 → 1.1 mg/m^2
1.1 mg/m^2 → 0.7 mg/m^2
0.7 mg/m^2 → Consider discontinuation

- Dose reduction should be considered for patients with hepatic impairment.
- Japanese pharmacopoeia physiological saline should be used to dilute eribulin mesilate.

(5) Post-marketing investigations

The applicant plans to conduct a specified use results survey covering all patients who receive eribulin mesilate (target sample size, 500; observation period, 1 year). The proposed key survey items are infections and bone marrow depression because bone marrow depression occurred frequently in clinical studies [see "4.(iii).B.(6) Post-marketing investigations" of Review Report (1)].

PMDA's conclusions after review of the submitted post-marketing surveillance plan (draft):

- The adverse events requiring special attention in patients receiving eribulin mesilate are bone marrow depression, peripheral nerve disorder, infections, hepatic function disorder, and interstitial lung disease. These are known adverse events of other tubulin-targeting drugs as well, and there are no other events specific to eribulin mesilate requiring special attention. The surveillance need not cover all patients as long as data are promptly collected. Nevertheless, because of limited safety data of Japanese patients submitted for the present application (96 subjects in total; 15 and 81 subjects in Japanese Studies E7389-J081-105 and E7389-J081-221, respectively), the applicant should conduct the post-marketing surveillance promptly to collect further safety information and provide it to healthcare professionals.
- The key survey items should include peripheral nerve disorder, hepatic function disorder, and interstitial lung disease, in addition to infections and bone marrow depression as proposed by the applicant. The survey should be planned in a way that facilitates the accumulation of information on these events.
- The proposed sample size and observation period are acceptable.

These conclusions were supported by the expert advisors at the Expert Discussion. The following comments were raised by the expert advisors:

- Since interstitial lung disease is one of the adverse events requiring special attention in patients receiving eribulin mesilate, the applicant should collect information on radiotherapy status (prior or concomitant radiotherapy) as well through the post-marketing surveillance.
- The applicant should review the post-marketing surveillance plan considering the following points:
  (a) Information including adverse drug reaction data should be collected promptly from the post-marketing surveillance. The obtained information should be analyzed early by interim analyses etc. to discuss the necessity of modifying the surveillance plan. The analysis results should be promptly communicated to healthcare professionals.
  (b) The surveillance should be designed to collect information in a way that accurately captures how eribulin mesilate is being used in clinical settings with the least possible bias.

Based on the Expert Discussion, PMDA advised the applicant to reconsider the post-marketing surveillance plan in terms of the following aspects:

- The surveillance should be designed to collect and analyze safety information of eribulin mesilate in patients previously or concurrently treated with radiotherapy (safety information especially regarding interstitial lung disease, radiation pneumonitis, and radiation recall reaction).
- The surveillance should also be designed to collect and analyze information on the relationship between "exposure to eribulin mesilate (frequency and duration of reduction, suspension, or discontinuation)" and "previous or new-onset hepatic impairment" or "the presence or absence of concomitant bone marrow depression."

The applicant agreed with the advice, and made the following comments:

- A total of 3 interim analyses are to be performed at 6-month intervals after the market launch to obtain the safety profile of eribulin mesilate in clinical use. The analyzed safety profile is to be communicated to healthcare professionals at the earliest possible time.
- Eribulin mesilate will be supplied to approximately 550 medical institutions, of which approximately 250 are expected to participate in the survey. The survey will cover all patients in the participating institutions who receive eribulin mesilate during the enrollment period, to avoid patient selection bias.

PMDA accepted the applicant's response. Instructions for the surveillance are to be given upon the approval of the product.

(6) Others

(6).1) Mechanism of action of eribulin mesilate

At the Expert Discussion, the following comments were raised by the expert advisors:

The submitted data do not clearly explain the mechanism of how eribulin mesilate achieves efficacy on taxane-resistant cells. The mechanism should continue to be investigated from the nonclinical aspect as well.

Because the mechanism in question has not been fully elucidated [see "3.(i).B.(2). Efficacy of eribulin mesilate" of Review Report (1)], PMDA advised the applicant to actively engage in nonclinical studies to clarify the mechanism, and to communicate new findings to healthcare professionals appropriately. The applicant agreed.

(6).2) Pharmacokinetics of eribulin

Comments of the expert advisors at the Expert Discussion:

According to the applicant, low CL levels in patients with hepatic impairment in Japanese Study E7389-J081-105 were attributed to diminished intrinsic clearance resulting from the decreased expression and activity levels of P-glycoprotein (P-gp), which is considered to be involved in biliary excretion of

eribulin [see "4.(ii).B.(1) Pharmacokinetic linearity of eribulin" of Review Report (1)]. However, Foreign Study E7389-E044-109 showed no marked effects of ketoconazole, a P-gp inhibitor, on the PK of eribulin [see "4.(ii).A.(6) Foreign phase I study (Foreign Study E7389-E044-109, February 2009 to July 2009)" of Review Report (1)]; therefore, whether P-gp-mediated elimination is the main cause of changes in CL is uncertain.

PMDA asked the applicant to conduct an additional investigation of the main cause of the decreased in CL of eribulin in light of the results of Foreign Study E7389-E044-109.

The applicant's response:
In Foreign Study E7389-E044-109, concomitant ketoconazole had no effect on the PK of eribulin. This was because ketoconazole has high inhibition constant for P-gp, and because ketoconazole concentration in the liver was not high enough to inhibit P-gp activity; this leaves the possibility of the involvement of P-gp in the PK of eribulin. Eribulin is a substrate of P-gp, as demonstrated in the studies using P-gp-deficient CF-1 mice, and is mainly excreted unchanged in feces as demonstrated in the foreign mass balance study (Foreign Study E7389-E044-103). These findings suggest that the elimination of eribulin depends largely on P-gp-mediated biliary excretion. However, there are no available data showing the extent of contribution of P-gp to the CL of eribulin. This issue, including the involvement of transporters other than P-gp, will be further investigated.

PMDA's view:
The applicant's explanation remains speculative because there are no data on ketoconazole concentrations in the liver in Foreign Study E7389-E044-109. Since the contribution of P-gp to eribulin clearance or the mechanism of biliary excretion have not been fully elucidated to date, the applicant's conclusion that changes in CL are mainly attributable to P-gp-mediated elimination is premature. The involvement of P-gp and other transporters in the PK of eribulin should be further studied, and new findings should be appropriately communicated to healthcare professionals.

(6).3) Per protocol population (PPP)

The applicant's report:
The on-site GCP inspection of Foreign Study E7389-G000-305 revealed exclusion of 2 subjects from the PPP despite their adherence to the protocol. Taking this opportunity, the applicant checked how subjects had been managed in Foreign Study E7389-G000-305, and found that 7 subjects were erroneously included in or excluded from the PPP.

The applicant explained that these errors did not affect efficacy evaluation, because the primary endpoint of Foreign Study E7389-G000-305 was OS in the intent-to-treat (ITT) population, and because the presence or absence of the 7 subjects in the PPP had little effect on the analysis results of OS in the PPP, a secondary endpoint.

PMDA examined the revised PPP analysis results and accepted the applicant's explanation.

III. Additions to Review Report (1)

(1) Additional data from long-term stability studies of the drug substance [2.A.(1).4) Stability of the drug substance of Review Report (1)]

Additional data from ongoing long-term stability studies using primary batches of the drug substance (–65°C, –20°C; up to 36 months; 3 batches) and commitment batches (–65°C, –20°C; up to 24 months for 3 batches and up to 36 months for 2 batches) were submitted. The data showed no effects of long-term storage on the quality of the dug substance under any of the storage conditions.

(2) Change in the pH control limit in the manufacturing process of the drug product [2.A.(2).3) Manufacturing process of Review Report (1)]

During the review of the new drug application for eribulin mesilate in the US, the lower limit of pH control values for the medicinal solution in Step [redacted] was changed from [redacted] to [redacted] based on actual measured values. In line with this, the applicant asked permission to change the mentioned values to [redacted] in the Japanese application as well. PMDA considered that the change would not affect quality control of the drug product, and accepted the change.

(3) Results of the Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

(3).1) PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection of the data submitted in the New Drug Application was conducted in accordance with the provisions of the Pharmaceutical Affairs Act. With no particular problems identified, PMDA concluded that there should be no problem in conducting a regulatory review based on the submitted application documents.

(3).2) PMDA's conclusion on the on-site GCP inspection results

An on-site GCP inspection was conducted in accordance with the Pharmaceutical Affairs Act for the data submitted in the New Drug Application (5.3.3.2.3, 5.3.5.1.1, and 5.3.5.2.3). The following findings were noted at some study sites: (1) some study activities were performed by physicians who had not been appointed by investigators to take an important role in the clinical study; (2) source data (ECG charts of some subjects) were not stored; (3) protocol deviations (failure to perform vital sign measurements, urinalysis, assessment of the Eastern Cooperative Oncology Group Performance Status, and ECG in some subjects); and (4) failure to obtain informed consent based on revised written information for continued participation in the study. These nonconformities indicated that the sponsor had failed to adequately monitor on-site study activities. A clinical study report revealed protocol

deviations in handling of some subjects (efficacy analysis PPP). However, PMDA concluded that there should be no problem in conducting a regulatory review based on the submitted data.

IV. Overall Evaluation

PMDA has concluded that the product may be approved for the indication, dosage, and administration shown below. The re-examination period is 8 years. The drug product and its drug substance are both classified as a poisonous drug and a powerful drug, but not as a biological product or a specified biological product.

[Indication]

Inoperable or recurrent breast cancer

[Dosage and administration]

The usual adult dosage is 1.4 mg/m^2 (body surface area) of eribulin mesilate administered intravenously over 2 to 5 minutes once weekly for 2 consecutive weeks, followed by a rest week. This treatment cycle is repeated. The dose may be adjusted according to the patient's condition.

[Warnings]

1. Anticancer chemotherapy including eribulin mesilate should be administered only to eligible patients by a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution well-prepared for emergencies. Prior to treatment with eribulin mesilate, the benefits and risks of treatment should be fully explained to the patient or his/her family before obtaining written consent.
2. Bone marrow depression may occur. The patient's condition should be closely monitored through frequent blood tests and other measures. The patient's eligibility should be carefully determined in light of the "Contraindications," "Careful Administration," and "Important Precautions" sections of the package insert.
   Read the package insert carefully before using eribulin mesilate.

[Contraindications]

1. Patients with severe bone marrow depression
2. Patients with a history of hypersensitivity to any of the components of the product
3. Pregnant or possibly pregnant women

[Precautions for Indication]

1. The efficacy and safety of eribulin mesilate for adjuvant or neoadjuvant chemotherapy have not been established.
2. Eribulin mesilate is indicated for patients with breast cancer that has worsened or recurred after chemotherapy including an anthracycline and a taxane.

[Precautions for Dosage and Administration]

1. The efficacy and safety of eribulin mesilate in combination with other antitumor drugs have not been established.
2. Delay or suspend administration or reduce the dose as needed according to the criteria below.

Recommended dose delays and reductions in Week 1 of each cycle

Start of treatment	Delay the dose if the patient does not meet the following requirements: • Neutrophil count ≥1000/mm^3 • Platelet count ≥75,000/mm^3 • Grade ≤2[Note 1)] non-hematological toxicity
Dose reduction	Use a reduced dose if any of the following has occurred in the previous treatment cycle[Note 2)]: • Neutrophil count decreased (<500/mm^3) lasting for >7 days • Neutrophil count decreased (<1000/mm^3) accompanied by fever or infection • Platelet count decreased (<25,000/mm^3) • Platelet count decreased (<50,000/mm^3) requiring blood transfusion • Grade ≥3[Note 1)] non-hematological toxicity • Suspension of treatment in the second week due to adverse reactions, etc.

Recommended dose delays, reductions, and suspension in Week 2 of each cycle

Start of treatment	Delay the dose if the patient does not meet the following requirements: • Neutrophil count ≥1000/mm^3 • Platelet count ≥75,000/mm^3 • Grade ≤2[Note 1)] non-hematological toxicity
Resumption	Resume the treatment at a reduced dose[Note 2)] if the starting criteria are met within 1 week after treatment delay.
Suspension	Suspend treatment if the starting criteria are not met within 1 week after treatment delay.

Note 1) Based on the Common Terminology Criteria for Adverse Events (CTCAE) v. 3.0

Note 2) Recommended dose reductions:

Before reduction → After reduction
1.4 mg/m^2 → 1.1 mg/m^2
1.1 mg/m^2 → 0.7 mg/m^2
0.7 mg/m^2 → Consider discontinuation

3. Dose reduction should be considered for patients with hepatic impairment.
4. Japanese pharmacopoeia physiological saline should be used to dilute eribulin mesilate.