Report on the Deliberation Results

February 24, 2016

Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health 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]	July 30, 2015

[Results of deliberation]

In the meeting held on February 1, 2016, the Second Committee on New Drugs concluded that the partial change application for 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 re-examination period is 10 years.

[Conditions for approval]

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

January 13, 2016
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]	July 30, 2015
[Dosage form/Strength]	Injectable solution: each vial (2.0 mL) contains 1.0 mg of eribulin mesilate
[Application classification]	Prescription drug, (4) Drug with a new indication
[Items warranting special mention]	Orphan drug (Drug Designation No. 341 of 2014 [*26 yaku*], PFSB/ELD Notification No. 0611-1 dated June 11, 2014, 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 13, 2016

[Brand name] Halaven Injection 1 mg
[Non-proprietary name] Eribulin Mesilate
[Applicant] Eisai Co., Ltd.
[Date of application] July 30, 2015
[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of soft tissue sarcoma has been demonstrated and its safety is acceptable in view of its observed benefits. However, further investigation will be necessary through post-marketing surveillance for the following: bone marrow depression, peripheral nerve disorder, infections, hepatic function disorder, interstitial lung disease, and QT/QTc prolongation.

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

[Indication] Inoperable or recurrent breast cancer and soft tissue sarcoma

(Words underlined are added.)

[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.

(No changes)

[Condition for approval] The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

December 1, 2015

I. Product Submitted for Registration

[Brand name]	Halaven Injection 1 mg
[Non-proprietary name]	Eribulin Mesilate
[Applicant]	Eisai Co., Ltd.
[Date of application]	July 30, 2015
[Dosage form/Strength]	Injectable solution: each vial (2.0 mL) contains 1.0 mg of eribulin mesilate
[Proposed indications]	Inoperable or recurrent breast cancer and soft tissue sarcoma

(Underline denotes addition.)

[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.

(No changes)

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. The present application is for a new indication, and no pharmacokinetic or toxicity data were submitted for the "Non-clinical data" section.

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 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.

In Japan, eribulin mesilate was approved in April 2011 for the indication of "inoperable or recurrent breast cancer."

1.(2) History of development

Outside Japan, the European Organization for Research and Treatment of Cancer (EORTC) initiated a phase II study in patients with STS previously treated with chemotherapy (Foreign Study E7389-E044-207) in [redacted] 20[redacted]. The purpose of the study was to develop eribulin mesilate for the treatment of soft tissue sarcoma (STS). The applicant then started a phase III study in patients with liposarcoma or leiomyosarcoma previously treated with chemotherapy (Foreign Study E7389-G000-309) in March 2011.

In the US and Europe, marketing applications for eribulin mesilate for the treatment of STS was filed in July 2015, based mainly on the results of Foreign Study E7389-G000-309. As of October 2015, the applications are under review, and eribulin mesilate has not been approved in any country or region for the indication of STS.

In Japan, the applicant started a phase II study in patients with STS previously treated with chemotherapy (Japanese Study E7389-J081-217) in November 2011.

The applicant has filed a partial change application for eribulin mesilate for an additional indication of STS, based mainly on the results of Japanese Study E7389-J081-217 and Foreign Study E7389-G000-309.

Eribulin mesilate was designated as an orphan drug in June 2014 with the intended indication of soft tissue sarcoma (Drug Designation No. 341 of 2014 [*26 yaku*]).

2. Non-clinical data

2.(i) Summary of pharmacology studies

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

Primary pharmacodynamics

Inhibition of cell proliferation in soft tissue sarcoma cell lines

2.(i).A.(1) *In vitro* (Reports CAIVT0105 and CAIVT0106)

The antiproliferative effect of eribulin mesilate on a MES-SA human uterine sarcoma cell line was evaluated based on the amount of cellular adenosine triphosphate (ATP). The IC_{50} value of eribulin mesilate against the MES-SA cell line was 1.99 ± 0.05 nmol/L (mean ± standard error; n = 3).

2.(i).A.(2) *In vivo* (Reports M[redacted]030, MT[redacted]35, and A[redacted]017)

The antiproliferative effect of eribulin mesilate was evaluated in athymic mice bearing a subcutaneous xenograft of a SK-LMS-1 human leiomyosarcoma cell line. From Day 7 post-xenografting (tumor volume, ≥300 mm^3), the mice received intravenous administration of eribulin mesilate 0.19, 0.38, 0.75, or 1.5 mg/kg once weekly (2 doses in total). The time (the number of days) to a 4-fold increase in tumor volume from baseline was calculated. The antiproliferative effect of eribulin mesilate was statistically

significantly higher in the 0.75 and 1.5 mg/kg groups than in the vehicle (saline) group (see the table below).

Antiproliferative effect of eribulin mesilate on the SK-LMS-1 cell line

Treatment group	Time to a 4-fold increase in tumor volume from baseline (days)
Vehicle	5.5 ± 1.64
Eribulin mesilate 0.19 mg/kg	12.3 ± 2.88
Eribulin mesilate 0.38 mg/kg	17.3 ± 1.63
Eribulin mesilate 0.75 mg/kg	19.5 ± 1.64*
Eribulin mesilate 1.5 mg/kg	> 21*

Mean ± standard deviation; n = 6; * $P < 0.05$ against the vehicle group (Dunnett's test)

Athymic mice bearing a subcutaneous xenograft of a HT-1080 human fibrosarcoma cell line were divided into treatment groups on Day 14 post-xenografting (the mean tumor volume in each group, 121-222 mm^3). The mice received intravenous administration of eribulin mesilate 1.27, 1.69, 2.25, 3, or 4 mg/kg or paclitaxel 20 mg/kg on Days 16, 20, and 24 post-xenografting. The time to a 2-fold increase in tumor volume from Day 14 post-xenografting was calculated. The antiproliferative effect was statistically significantly higher in the eribulin mesilate 1.27 and 1.69 mg/kg groups than in the vehicle (saline) group (see the table below). All the mice in the eribulin mesilate 2.25, 3, and 4 mg/kg groups were withdrawn from the study due to decreased body weight caused by eribulin mesilate.

Antiproliferative effect of eribulin mesilate on the HT-1080 cell line

Treatment group	Time to a 2-fold increase in tumor volume from Day 14 post-xenografting (days)
Vehicle	6 (3, 14)
Eribulin mesilate 1.27 mg/kg	– (50, 84)*
Eribulin mesilate 1.69 mg/kg	– (50, 84)*
Paclitaxel 20 mg/kg	35 (21, 84)*

Median (range [the maximum value was obtained on the final evaluation day]); n = 10;
–, Not calculated because 1 mouse receiving 1.27 mg/kg and 3 mice receiving 1.69 mg/kg showed a 2-fold increase in tumor volume on the final evaluation day (Day 98 post-xenografting) from Day 14 post-xenografting.
*$P < 0.0001$ against the vehicle group (log-rank test)

Eribulin mesilate 0.875, 1.75, or 3.5 mg/kg or vincristine sulfate (vincristine) was administered intravenously once weekly (2 doses in total) to athymic mice bearing a subcutaneous xenograft of an A673 human Ewing's sarcoma cell line from Day 8 post-xenografting (the mean tumor volume in each group, 316.1-330.6 mm^3). Tumor volumes at Day 22 post-xenografting were calculated. The antiproliferative effect was statistically significantly higher in all the eribulin mesilate groups than in the vehicle (saline) group (see the table below).

Antiproliferative effect of eribulin mesilate on the A673 cell line

Treatment group	Tumor volume (mm^3)
Vehicle	5938.7 ± 714.0
Eribulin mesilate 0.875 mg/kg	23.7 ± 13.4*
Eribulin mesilate 1.75 mg/kg	22.2 ± 23.5*
Eribulin mesilate 3.5 mg/kg	15.3 ± 17.7*
Vincristine 0.375 mg/kg	4165.0 ± 1163.9*
Vincristine 0.75 mg/kg	2233.4 ± 527.8*
Vincristine 1.5 mg/kg	75.7 ± 58.1*

Mean ± standard deviation; n = 6; * $P < 0.05$ against the vehicle group (Dunnett's test)

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

PMDA's conclusion:

Eribulin mesilate is expected to be effective in the treatment of STS based on the data submitted for the present application, and in light of the antiproliferative effect of eribulin mesilate on malignant tumors confirmed during the regulatory review for the initial approval of the drug (see the "Review Report on Halaven Injection 1 mg dated January 12, 2011").

2.(ii) Summary of pharmacokinetic studies

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

No data from pharmacokinetic studies were submitted for the present application.

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

2.(ii).B.(1) Transporter-mediated pharmacokinetic interactions

Data submitted for the initial application of eribulin mesilate included evaluation of pharmacokinetic interactions mediated by human P-glycoprotein (P-gp), but did not include evaluation of pharmacokinetic interactions mediated by other transporters. The applicant had noted that they would continue to evaluate the pharmacokinetic interactions mediated by transporters other than P-gp (see the "Review Report on Halaven Injection 1 mg dated January 12, 2011").

PMDA asked the applicant to provide findings regarding the pharmacokinetic interactions mediated by transporters other than P-gp.

The applicant's response:

After the approval of the initial application, pharmacokinetic interactions mediated by transporters other than P-gp were investigated. The results are as follows:

- OATP1B1-mediated transport of eribulin mesilate (0.3-10 μmol/L) was investigated in a HEK293 human fetal kidney cell line and a Chinese hamster ovary (CHO) cell line, both expressing the human organic anion transporting polypeptide (OATP) 1B1. The amount of intracellular uptake of eribulin mesilate was higher in the CHO cell line expressing OATP1B1 than in a CHO cell line not expressing OATP1B1, but an OATP1B1 inhibitor (rifampicin 100 μmol/L) did not inhibit intracellular uptake of eribulin mesilate. Meanwhile, no marked difference was detected in the

amount of intracellular uptake of eribulin mesilate between the HEK293 cell lines with and without OATP1B1 expression.

- OCT1-mediated transport of eribulin mesilate (0.3-10 μmol/L) was investigated in a S_2 mouse renal proximal tubule cell line and a CHO cell line, both expressing the human organic cation transporter (OCT) 1. The amount of intracellular uptake of eribulin mesilate was higher in the S_2 cell line expressing OCT1 than in a S_2 cell line not expressing OCT1. Meanwhile, no marked difference was detected in the amount of intracellular uptake of eribulin mesilate between the CHO cell lines with and without OCT1 expression; OCT1 inhibitors (cimetidine 1 mmol/L, verapamil 100 μmol/L) did not inhibit the intracellular uptake of eribulin mesilate.
- Transporter-mediated transport of eribulin mesilate was investigated in the following cell lines: a S_2 cell line and a CHO cell line, both expressing the human organic anion transporter (OAT) 1; a S_2 cell line and a HEK293 cell line, both expressing OAT3; CHO cell lines expressing OATP1B3 or OCT2; and a MDCKII canine kidney cell line expressing the human multidrug and toxin extrusion protein transporter (MATE) 1 (eribulin mesilate doses: 0.3-3 μmol/L for MATE1; 0.3-10 μmol/L for other transporters). None of the cell lines showed marked difference in the amount of intracellular uptake of eribulin mesilate between cell lines with and without transporter expression.
- Breast cancer-resistant proteins (BCRP)-mediated transport of eribulin mesilate (0.3-10 μmol/L) was investigated in a LLC-PK1 pig kidney cell line and a MDCKII cell line, both expressing human BCRP. The transport was evaluated by the $P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$ ratio (the ratio of the apparent basal-to-apical permeability coefficient to the apparent apical-to-basal permeability coefficient). The results showed no marked difference in the $P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$ ratio of eribulin mesilate between cell lines with and without BCRP expression.
- Transporter-mediated transport of eribulin mesilate (3 and 10 μmol/L) was investigated in membrane vesicles prepared from Sf9 insect ovarian cell lines expressing human bile salt export pump (BSEP) or human multidrug resistance-associated protein (MRP) 2 or from a LLC-PK1 cell line expressing MRP4. No marked difference was detected in the amount of uptake of eribulin mesilate into the membrane vesicle between membrane vesicles with and without transporter expression. The ATP-dependent transport activity of eribulin mesilate (0.3 and 1 μmol/L) was investigated in membrane vesicles prepared from a Sf9 cell line expressing MRP2, a HEK293 cell line expressing MRP4, or a Hi5 insect cell line expressing BSEP. The transport activity was evaluated by the ATP/adenosine monophosphate (AMP) ratio. The results showed no marked difference in the transport activity of eribulin mesilate between membrane vesicles with and without transporter expression.
- The inhibitory action of eribulin mesilate (0.1-10 μmol/L) on OATP1B1-mediated transport of substrates was investigated in a HEK293 cell line expressing OATP1B1. The results showed that 10 μmol/L eribulin mesilate inhibited the transport of OATP1B1 substrates by 28.2%.
- The inhibitory action of eribulin mesilate (0.01-10 μmol/L) on OATP1B3-mediated transport of substrates was investigated in a CHO cell line expressing OATP1B3. The results showed that 10 μmol/L eribulin mesilate inhibited the transport of OATP1B3 substrates by 26.1%.

- The inhibitory action of eribulin mesilate (0.1-10 μmol/L) on transporter-mediated transport of substrates was investigated in membrane vesicles prepared from the following cell lines: S_2 cell lines expressing OAT1 or OAT3; a S_2 cell line and a CHO cell line, both expressing OCT1; a CHO cell line expressing OCT2; a MDCKII cell line expressing MATE1; and a Sf9 cell line expressing BCRP. Eribulin mesilate, even at the highest concentration examined, did not markedly inhibit the transport of substrates of any of the transporters.
- The inhibitory action of eribulin mesilate (0.01-10 μmol/L) on transporter-mediated transport of substrates was investigated in membrane vesicles prepared from a Sf9 cell line expressing BSEP or MRP2 or from a LLC-PK1 cell line expressing MRP4. Eribulin mesilate, even at the highest concentration examined, did not markedly inhibit the transport of substrates of any of the transporters.

These investigations suggested that eribulin mesilate is not a substrate of BCRP, BSEP, MATE1, MRP2, MRP4, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2. The C_{max} following repeated doses of eribulin mesilate 1.4 mg/m^2 to Japanese patients with solid tumors was 544.4 ng/mL (0.746 μmol/L) (see the "Review Report on Halaven Injection 1 mg dated January 12, 2011"). Given these facts, eribulin mesilate is unlikely to cause pharmacokinetic interactions by inhibiting BCRP, BSEP, MATE1, MRP2, MRP4, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2 in clinical use.

PMDA accepted the applicant's explanation.

3. Clinical data

3.(i) Summary of clinical pharmacology studies

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

The pharmacokinetics (PK) of eribulin were studied in patients with cancer who received eribulin mesilate monotherapy.

3.(i).A.(1) Japanese phase II study (5.3.5.2.2, Japanese Study E7389-J081-217 [ongoing since November 2011, data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study is underway in 52 patients with unresectable soft tissue sarcoma (STS) previously treated with chemotherapy (PK analysis population, 42 patients) to investigate the efficacy and safety of eribulin mesilate. Eribulin mesilate 1.4 mg/m^2 was administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle. Plasma concentrations of eribulin on Day 1 of Cycles 1 and 2 were determined. A population pharmacokinetic (PPK) analysis was conducted using the PK data from the patients [see "3.(i).A.(4) Population pharmacokinetic (PPK) analysis"].

3.(i).A.(2) Foreign phase II study (5.3.5.2.1, Foreign Study E7389-E044-207 [from [redacted], 20[redacted] to [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in 128 patients with unresectable STS previously treated with chemotherapy (PK analysis population, 125 patients) to investigate the efficacy and safety

of eribulin mesilate. Eribulin mesilate 1.4 mg/m^2 was administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle. Plasma concentrations of eribulin on Day 1 of Cycle 1 were determined. A PPK analysis was conducted using the PK data from the patients [see "3.(i).A.(4) Population pharmacokinetic (PPK) analysis"].

3.(i).A.(3) Foreign phase III study (5.3.5.1.1, Foreign Study E7389-G000-309 [ongoing since March 2011, data cut-off on [redacted], 20[redacted]])

An open-label, randomized, comparative study is being conducted in 452 patients with unresectable liposarcoma or leiomyosarcoma previously treated with chemotherapy (PK analysis population, 211 patients) to compare the efficacy and safety of eribulin mesilate and dacarbazine (DTIC). Eribulin mesilate 1.4 mg/m^2 was administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle. Plasma concentrations of eribulin on Day 1 of Cycles 1 and 2 were determined. A PPK analysis was conducted using the PK data from the patients [see "3.(i).A.(4) Population pharmacokinetic (PPK) analysis"].

3.(i).A.(4) Population pharmacokinetic (PPK) analysis

A PPK analysis using a nonlinear mixed effect model (software used, NONMEM version 7.2) was conducted on PK data (n = 478; 4566 observations) obtained from phase I studies in patients with advanced solid tumors (Japanese Study E7389-J081-105, Foreign Studies E7389-A001-101, E7389-A001-102, E7389-E044-108, E7389-E044-109, and E7389-E044-110), phase II studies in patients with STS (Japanese Study E7389-J081-217 and Foreign Study E7389-E044-207), and a phase III study (Foreign Study E7389-G000-309). The PK of eribulin was described using a 3-compartment model with first-order elimination.

Candidate covariates for a PK parameter (clearance [CL]) of eribulin were age, body weight, sex, race, Eastern Cooperative Oncology Group performance status, serum albumin concentration, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine clearance, and cancer type. Body weight, serum albumin concentration, and total bilirubin were selected as significant covariates on CL, as they were in the PPK analysis submitted for the initial application (see the "Review Report on Halaven Injection 1 mg dated January 12, 2011"). The final model included body weight as the covariate on the distribution volume of the central compartment (V1), distribution volumes of the peripheral compartments 2 and 3 (V2 and V3), and the clearances between the central compartment and the peripheral compartments 2 and 3 (Q2 and Q3).

3.(i).A.(5) Relationships between eribulin exposure and efficacy or safety

3.(i).A.(5).1) Relationship between eribulin exposure and efficacy

Eribulin exposure (AUC) was estimated from the above PPK model based on the results of a Japanese phase II study (Japanese Study E7389-J081-217) and a foreign phase III study (Foreign Study E7389-G000-309) in patients with STS [see "3.(i).A.(4) Population pharmacokinetic (PPK) analysis"]. The relationship between eribulin exposure (AUC) and the following endpoints were investigated: overall

survival (OS), progression free survival (PFS), progression free rate at Week 12 (PFR_{12wks}), best overall response, and change from baseline in the sum of the longest diameter of the target lesions. The results showed no relationship between AUC and any of these endpoints.

3.(i).A.(5).2) Relationship between eribulin exposure and the incidence of adverse events

Eribulin exposure (AUC and cumulative AUC) was estimated from the above PPK model [see "3.(i).A.(4) Population pharmacokinetic (PPK) analysis"]. Based on the results of a Japanese phase II study (Japanese Study E7389-J081-217) and a foreign phase III study (Foreign Study E7389-G000-309) in patients with STS, the relationship between the estimated eribulin exposure (AUC and cumulative AUC) and the incidences of Grade ≥3 adverse events (Grade ≥3 fatigue, nausea, anaemia, febrile neutropenia, and neuropathy peripheral*) were investigated. The cumulative AUC in subjects with Grade ≥3 neuropathy peripheral (n = 6) tended to be higher than that in subjects without Grade ≥3 neuropathy peripheral (n = 247). The applicant explained that definite conclusions cannot be drawn regarding the relationship between eribulin exposure and the incidence of neuropathy peripheral because of the extremely small number of subjects experiencing Grade ≥3 neuropathy peripheral. No clear relationships were observed between eribulin exposure and the incidence of Grade ≥3 fatigue, nausea, anaemia, or febrile neutropenia.

* "Neuropathy peripheral" included MedDRA preferred terms of peripheral sensory neuropathy, peripheral motor neuropathy, and polyneuropathy (MedDRA/J, ver. 17.1).

3.(i).A.(5).3) Relationship between eribulin exposure and changes in QTc interval

Based on the results of a Japanese phase II study (Japanese Study E7389-J081-217) and a foreign phase III study (Foreign Study E7389-G000-309) in patients with STS, the relationship between plasma eribulin concentrations and changes from baseline in QT interval corrected using Fridericia's correction (QTcF) was evaluated using a linear model. The estimated slope (95% confidence interval [CI]) in a linear model for plasma eribulin concentrations and QTcF was −3.73 (−9.53, 2.07) μsec/ng/mL, showing no clear relationship between plasma eribulin concentrations and changes from baseline in QTcF.

3.(i).A.(6) Discussion of the applicant

3.(i).A.(6).1) Differences in the pharmacokinetics of eribulin between Japanese and non-Japanese patients with STS

The applicant explained that there are no clear difference in the PK of eribulin between Japanese and non-Japanese patients with STS, based on the following fact:

The table below shows plasma eribulin concentrations obtained on Day 1 of Cycles 1 and 2 in a Japanese phase II study (Japanese Study E7389-J081-217) and a foreign phase III study (Foreign Study E7389-G000-309) in patients with STS. No clear difference was observed between Japanese and non-Japanese patients with STS in the distribution of plasma eribulin concentrations up to 168 hours post-dose. In the PPK analysis, race was not selected as a significant covariate for the PK parameter (CL) of eribulin [see "3.(i).A.(4) Population pharmacokinetic (PPK) analysis"].

Plasma eribulin concentrations in Japanese and non-Japanese patients (ng/mL)

Cycle	Time point	n	Japanese Study E7389-J081-217 Japanese patients	n	Foreign Study E7389-G000-309 Non- Japanese patients
1	C_{max}*1	41	533 ± 135	59	448 ± 181
	C_{trough}*2	27	0.616 ± 0.303	93	0.591 ± 0.500
2	C_{max}*1	34	557 ± 148	50	453 ± 201
	C_{trough}*2	21	0.633 ± 0.305	81	0.708 ± 0.817

Mean ± standard deviation
*1 Plasma eribulin concentration measured within 7.2 minutes post- dose
*2 Plasma eribulin concentration measured between 162 and 174 hours post-dose

3.(i).A.(6).2) Pharmacokinetics of eribulin in patients with STS and those with breast cancer

The applicant explained that there is no clear difference in the PK of eribulin between patients with STS and those with breast cancer based on the following evidence:

The mean ± standard deviation of the C_{max}* of eribulin on Day 1 of Cycle 1 was 448 ± 181 ng/mL in a foreign phase III study in patients with STS (Foreign Study E7389-G000-309), and was 554 ± 598 ng/mL in a foreign phase II study in patients with breast cancer (Foreign Study E7389-G000-211). There was no clear difference in the distribution of plasma eribulin concentrations up to 168 hours post-dose between patients with STS and those with breast cancer.

* Plasma concentrations of eribulin measured within 7.2 minutes after dosing.

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

Based on the submitted data, PMDA accepted the applicant's explanations on the relationship between eribulin exposure and efficacy or safety, difference in the PK of eribulin between Japanese and non-Japanese patients, and difference in the PK of eribulin between patients with different cancer types.

3.(ii) Summary of clinical efficacy and safety

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

The applicant submitted efficacy and safety evaluation data: the results from 1 Japanese phase II study, 1 foreign phase II study, and 1 foreign phase III study.

List of clinical studies evaluating efficacy and safety

Data type	Study region	Study identifier	Phase	Target patients	No. of patients enrolled	Dosage and administration	Main endpoints
Evaluation data	Japanese	E7389-J081-217	II	Patients with STS previously treated with chemotherapy	52	Eribulin mesilate 1.4 mg/m^2 was administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle.	Efficacy Safety
	Foreign	E7389-E044-207	II	Patients with STS previously treated with chemotherapy	128	Eribulin mesilate 1.4 mg/m^2 was administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle.	Efficacy Safety
		E7389-G000-309	III	Patients with liposarcoma or leiomyosarcoma previously treated with chemotherapy	594* (a) 228 (b) 224	(a) Eribulin mesilate 1.4 mg/m^2 was administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle; or (b) DTIC 850, 1000, or 1200 mg/m^2 was administered intravenously on Day 1 of a 3-week cycle.	Efficacy Safety

STS, soft tissue sarcoma; * Including 452 patients who were randomized

Each clinical study is summarized in the subsequent section.

The main adverse events excluding deaths reported in each clinical study are presented in "3.(iii) Adverse events and other relevant findings observed in clinical studies," and the PK-related study results are presented in "3.(i) Summary of clinical pharmacology studies."

3.(ii).B Evaluation data

3.(ii).B.(1) Japanese study

Japanese phase II study (5.3.5.2.2, Japanese Study E7389-J081-217 [ongoing since November 2011, data cut-off on [redacted], 20[redacted]])

An open-label, uncontrolled study is being conducted in patients with unresectable STS[*1] previously treated with chemotherapy[*2] (target sample size, 35 patients with liposarcoma or leiomyosarcoma and ≥16 to ≤20 patients with other histological types) in 13 centers in Japan to investigate the efficacy and safety of eribulin mesilate. Eribulin mesilate 1.4 mg/m^2 was administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle. The treatment was continued until the patient experienced disease progression or met other study discontinuation criteria.

[*1] Patients with STS of any of the following histological types are ineligible for the study: embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing's sarcoma/primitive neuroectodermal tumor, gastrointestinal stromal tumor, dermatofibrosarcoma protuberans, inflammatory myofibroblastic tumor, neuroblastoma, malignant mesothelioma, and uterine mixed mesodermal tumor.

[*2] Patients previously treated with ≥1 chemotherapy regimen including an anthracycline or ifosfamide are eligible for the study.

Of 52 enrolled subjects, 1 did not receive eribulin mesilate due to infection and uncontrollable anemia. The remaining 51 subjects (35 with liposarcoma or leiomyosarcoma and 16 with STS of other

histological types) were included in the full analysis set (FAS). The FAS was the analysis population for efficacy and safety.

The efficacy analysis revealed that the PFR_{12wks} [two-sided 90% CI] by independent review of images was 60.0% [44.7%, 74.0%] (21 of 35 subjects) ($P < 0.0001$; accurate one-sided one-sample test on the pre-specified threshold*; one-sided significance level of 0.05) in subjects with liposarcoma or leiomyosarcoma, and 31.3% [13.2%, 54.8%] (5 of 16 subjects) ($P = 0.0790$; accurate one-sided one-sample test on the pre-specified threshold*) in subjects with STS of other histological types.

* The threshold PFR_{12wks} is 20% in patients with liposarcoma or leiomyosarcoma and 15% in patients with STS of other histological types. These thresholds were defined based on the recommended variables in the phase II study of STS initiated by the European Organization for Research and Treatment of Cancer (EORTC) (*Eur J Cancer*. 2002;38:543-9).

The safety analysis revealed a death of 1 of 51 subjects (2.0%) during the treatment period or the follow-up period (within 30 days after the last dose of eribulin mesilate). The cause of the death was cardiac failure, and a causal relationship with eribulin mesilate was ruled out for the death.

3.(ii).B.(2) Foreign studies

3.(ii).B.(2).1) Foreign phase II study (5.3.5.2.1, Foreign Study E7389-E044-207 [from [redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 148 patients with unresectable STS*1 previously treated with chemotherapy*2 (target sample size, 37 patients [17 in Stage 1, 20 in Stage 2] each with liposarcoma, leiomyosarcoma, synovial sarcoma, or STS of other histological types) in 15 centers in 5 foreign countries, to investigate the efficacy and safety of eribulin mesilate. Eribulin mesilate 1.4 mg/m^2 was administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle. The treatment was continued until the patient experienced disease progression or met other study discontinuation criteria.

*1 Patients with STS of any of the following histological types were ineligible for the study: embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing's sarcoma/primitive neuroectodermal tumor, gastrointestinal stromal tumor, dermatofibrosarcoma protuberans, inflammatory myofibroblastic tumor, neuroblastoma, malignant mesothelioma, and uterine mixed mesodermal tumor.

*2 Patients previously treated with 1 combination chemotherapy regimen or ≤2 single-agent chemotherapy regimens were eligible for the study.

Of 128 enrolled subjects, 1 did not receive eribulin mesilate because of brain metastasis detected before the start of study treatment. The remaining 127 subjects were included in the FAS. Of the 127 subjects, 115 were treated with ≥1 dose of eribulin mesilate and assessed as eligible for efficacy evaluation by the central assessment (32 with liposarcoma, 38 with leiomyosarcoma, 19 with synovial sarcoma, and 26 with other histological types of STS). The 115 subjects were thus included in the efficacy analysis population. The safety analysis population was the FAS.

Simon's two-stage design was used for efficacy assessment [see "3.(ii).C.(3).2) Target histological types and indication of eribulin mesilate"]. According to independent review of images,* the PFR_{12wks} (one-sided 90% CI [lower limit]) was 46.9% (34.5%) (15 of 32 subjects) in subjects with liposarcoma, 31.6%

(21.6%) (12 of 38 subjects) in subjects with leiomyosarcoma, 21.1% (9.5%) (4 of 19 subjects) in subjects with synovial sarcoma, and 19.2% (9.7%) (5 of 26 subjects) in subjects with STS of other histological types.

[*] Images were evaluated every 6 weeks, and images obtained at baseline and Week 12 were assessed not only by the investigator but also by the independent review board.

The safety results showed deaths in 3 subjects during the treatment period or the follow-up period (within 30 days after the last dose of eribulin mesilate). The cause of each death was malignant pleural effusion, general physical health deterioration, and cerebral ischaemia in 1 subject each. A causal relationship to eribulin mesilate could not be ruled out for cerebral ischaemia.

3.(ii).B.(2).2) Foreign phase III study (5.3.5.1.1, Foreign Study E7389-G000-309 [ongoing since March 2011, data cut-off on [redacted], 20[redacted]])

An open-label, randomized, comparative study is being conducted in patients with unresectable liposarcoma or leiomyosarcoma previously treated with chemotherapy[*] (target sample size, 450) in 139 centers in 23 foreign countries to compare the efficacy and safety of eribulin mesilate and DTIC.

[*] Patients previously treated with ≥2 chemotherapy regimens including ≥1 regimen of an anthracycline are eligible for the study.

In the eribulin mesilate group, eribulin mesilate 1.4 mg/m^2 was administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle. The treatment was continued until the patient experienced disease progression or met other study discontinuation criteria. In the DTIC group, DTIC was administered intravenously at 850, 1000, or 1200 mg/m^2 [*1] on Day 1 of a 3-week cycle. All 452 randomized subjects (228 in the eribulin mesilate group and 224 in the DTIC group) were included in the FAS. The efficacy analysis population was the FAS. In the FAS, 2 subjects (1 each in the eribulin mesilate group and the DTIC group) did not receive the study drug. The remaining 450 subjects (226 in the eribulin mesilate group and 224[*2] in the DTIC group) were included in the safety analysis population.

[*1] Before randomization, the investigators selected a dose level (850, 1000, or 1200 mg/m^2) for each subject according to his/her clinical condition to ensure safety, based on the results of a foreign phase II study in patients with unresectable STS (*Invest New Drugs.* 2008;26:175-81, *Ann Oncol.* 1991;2:307-9).

[*2] One subject assigned to the eribulin mesilate group received DTIC instead of eribulin mesilate. The subject was included in the DTIC group for the safety analysis.

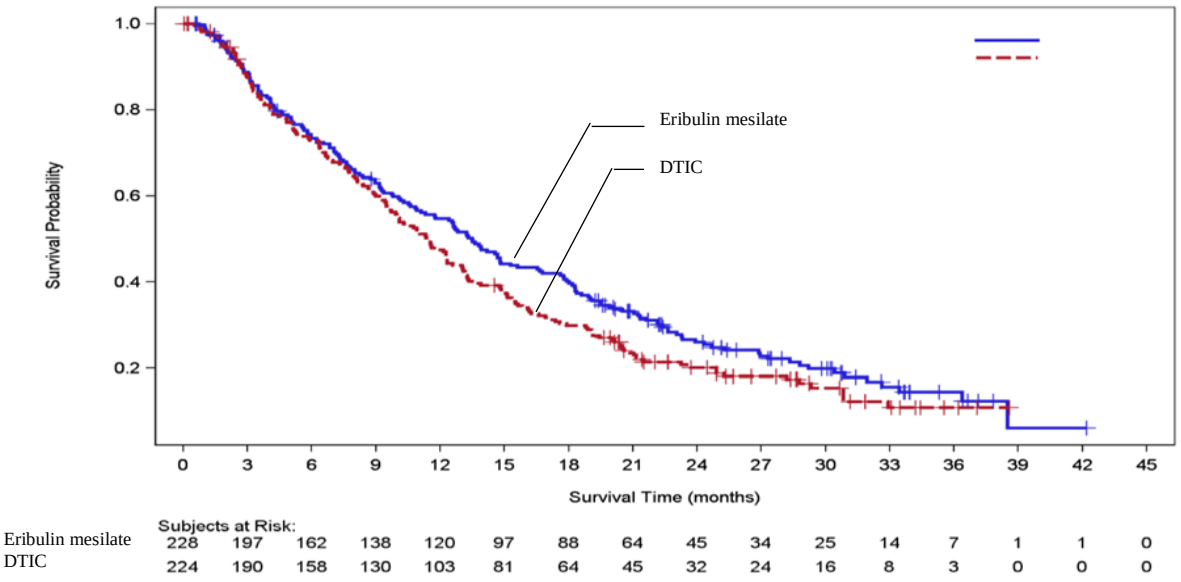
The primary endpoint of the study was overall survival (OS). In the study, an interim analysis was performed to evaluate the efficacy of treatment after 70% of the target number of events (247 of 353 events) had been reported. Probability of type I errors in the interim analysis was adjusted using the O'Brien-Fleming type alpha spending function based on the Lan-DeMets method. After the interim analysis, the independent data monitoring committee recommended continuing the study.

The final OS analysis results are shown in the table below, and Kaplan-Meier curves of OS in the figure below.

The final OS analysis results (Foreign Study E7389-G000-309, FAS, data cut-off on [redacted], 20[redacted])

	Eribulin mesilate	DTIC
n	228	224
Number of deaths (%)	176 (77.2)	181 (80.8)
Median [95% CI] (months)	13.5 [10.9, 15.6]	11.5 [9.6, 13.0]
Hazard ratio[*1] [95% CI]	0.768 [0.618, 0.954]	
P-value (2-sided)[*2,*3]	0.0169	

[*1] Cox regression model adjusted for stratification factors (histological type, geographical region, number of prior chemotherapy regimens [2, ≥ 3]);
[*2] A log-rank test stratified by histological type, geographical region, number of prior chemotherapy regimens (2, ≥ 3);
[*3] Significance level (two-sided) of 0.0455



Kaplan-Meier curves for the final OS analysis
(Foreign Study E7389-G000-309, FAS, data cut-off on [redacted], 20[redacted])

The safety results showed deaths of 15 subjects in the eribulin mesilate group and 9 subjects in the DTIC group during the treatment period or the follow-up period (within 30 days after the last dose of study drug). The causes of deaths in the eribulin mesilate group were disease progression in 5 subjects and respiratory failure, disease progression/respiratory failure, neutropenic sepsis, acute respiratory failure, intestinal obstruction, pneumonia aspiration, general physical health deterioration, large intestine perforation, septic shock, and metastases to lung in 1 subject each. In the DTIC group, the causes of deaths were disease progression in 4 subjects, unknown in 2 subjects, and disease progression/respiratory failure, general physical health deterioration, and cardiac arrest in 1 subject each. A causal relationship to the study drug could not be ruled out for neutropenic sepsis in the eribulin mesilate group.

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

3.(ii).C.(1) Efficacy

Based on the following reviews, PMDA concluded that the efficacy of eribulin mesilate was demonstrated in patients with STS in Foreign Study E7389-G000-309.

3.(ii).C.(1).1) Selection of the control

The applicant's rationale for selecting DTIC as the control in Foreign Study E7389-G000-309 in patients with unresectable liposarcoma or leiomyosarcoma previously treated with ≥2 chemotherapy regimens including ≥1 regimen with an anthracycline:

When Foreign Study E7389-G000-309 was being planned, the US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Soft Tissue Sarcoma (NCCN Guidelines) (v.2.2010) recommended the following therapeutic options for patients with unresectable STS: a monotherapy or combination therapy with an anthracycline, ifosfamide, gemcitabine hydrochloride, DTIC, or other antitumor agents. Meanwhile, the European Society for Medical Oncology Clinical Practice Guidelines, Soft Tissue and Visceral Sarcomas (ESMO Guidelines) 2010 (*Ann Oncol.* 2010;21(suppl 5):v198-203) recommended the following treatment options for patients who had received the initial chemotherapy with an anthracycline or who are ineligible for anthracycline therapy: a monotherapy with ifosfamide, trabectedin, gemcitabine hydrochloride, or DTIC, or combination therapy with gemcitabine hydrochloride and docetaxel. For the indication of STS, doxorubicin (DXR) had been approved in the US, and DTIC and trabectedin in the EU.

As stated above, DTIC had already been a common drug among patients included in Foreign Study E7389-G000-309 in the countries and regions involved. Therefore, DTIC was selected as the control in the study.

PMDA's view:

The applicant's explanation is generally acceptable. However, in Foreign Study E7389-G000-309, the investigators selected a dose level (i.e. 850, 1000, or 1200 mg/m^2) for each subject ("the DTIC 850 mg/m^2 cohort," "the DTIC 1000 mg/m^2 cohort," or "the DTIC 1200 mg/m^2 cohort") according to their clinical condition before randomization [see "3.(ii).B.(2).2) Foreign phase III study"]. The selection of dose levels of DTIC may have affected the efficacy evaluation of eribulin mesilate. Therefore, the efficacy of each dose level of DTIC selected before randomization should be evaluated.

3.(ii).C.(1).2) Efficacy endpoint and evaluation results

Patients with unresectable STS receive treatments to prolong their lives. PMDA therefore considers that OS is the appropriate primary endpoint of Foreign Study E7389-G000-309.

The efficacy results showed that the OS in the eribulin mesilate group was statistically significantly longer than that in the DTIC group in Foreign Study E7389-G000-309 [see "3.(ii).B.(2).2) Foreign phase III study"].

The table below presents the results of the final OS analysis by DTIC dose level selected before randomization. There was no clear difference in OS among subjects receiving DTIC regardless of dose level selected before randomization. Meanwhile, (a) the hazard ratio in the DTIC 850 mg/m^2 cohort was

≥ 1 and (b) the OS in subjects receiving eribulin mesilate in the DTIC 850 mg/m^2 cohort tended to be shorter than that in subjects receiving eribulin mesilate in the other DTIC cohorts. The applicant explained that these results may have been attributable to the number of treatment cycles, for the following reasons:

- In the DTIC 850 mg/m^2 cohort, the number of treatment cycles (median [minimum, maximum]) was smaller in the eribulin mesilate group (2.0 [1.0, 31.0]) than in the DTIC group (4.0 [1.0, 11.0]).
- The number of treatment cycles (median [minimum, maximum]) in the eribulin mesilate group was smaller in the DTIC 850 mg/m^2 cohort than in the other DTIC cohorts: 2.0 (1.0, 31.0) in the 850 mg/m^2 cohort; 4.0 (1.0, 34.0) in the 1000 mg/m^2 cohort; and 3.0 (1.0, 22.0) in the 1200 mg/m^2 cohort.

The final OS analysis results by DTIC dose level selected before randomization (Foreign Study E7389-G000-309, FAS, data cut-off on [redacted], 20[redacted])

DTIC dose level selected	Eribulin mesilate			DTIC			Hazard ratio* [95% CI]
	n	Number of deaths (%)	Median [95% CI] (months)	n	Number of deaths (%)	Median [95% CI] (months)	
850 mg/m^2	53	45 (84.9)	10.5 [7.5, 13.9]	47	40 (85.1)	12.3 [7.8, 17.6]	1.041 [0.643, 1.687]
1000 mg/m^2	136	100 (73.5)	16.5 [11.8, 19.5]	141	110 (78.0)	11.6 [9.5, 13.5]	0.725 [0.544, 0.965]
1200 mg/m^2	39	31 (79.5)	12.4 [7.6, 15.3]	36	31 (86.1)	10.3 [5.1, 12.3]	0.792 [0.447, 1.402]

* Cox regression model adjusted for stratification factors (histological type, geographical region, number of prior chemotherapy regimens [2, ≥ 3])

The final OS analysis results by histological type are shown in the table below.

The final OS analysis results by histological type (Foreign Study E7389-G000-309, FAS, data cut-off on [redacted], 20[redacted])

Histological type	Eribulin mesilate			DTIC			Hazard ratio* [95% CI]
	n	Number of deaths (%)	Median [95% CI] (months)	n	Number of deaths (%)	Median [95% CI] (months)	
Liposarcoma	71	52 (73.2)	15.6 [10.2, 18.6]	72	63 (87.5)	8.4 [5.2, 10.1]	0.511 [0.346, 0.753]
Leiomyosarcoma	157	124 (79.0)	12.7 [9.8, 14.8]	152	118 (77.6)	13.0 [11.3, 15.1]	0.927 [0.714, 1.203]

* Cox regression model adjusted for stratification factors (geographical region, number of prior chemotherapy regimens [2, ≥ 3])

Initially, statistical analysis program tests (Dry Runs) were planned to be performed with data from simulated treatment groups. However, actual treatment data from Foreign Study E7389-G000-309 were analyzed in a total of 6 Dry Runs after 293 OS events had been reported.

The applicant's explanation on the matter:

The table below shows the OS in the interim analysis, Dry Runs, and the final analysis. The table also shows the two-sided significance levels when each Dry Run was regarded as an interim analysis and the probability of type I error in interim analyses was adjusted using the O'Brien-Fleming type alpha spending function based on the Lan-DeMets method. The results support the applicant's view that the final analysis results showed a statistically significant difference.

OS results in the interim analysis, Dry Runs, and final analysis (FAS) and significance levels when each Dry Run was regarded as an interim analysis

Analysis time point	Number of events			Hazard ratio [95% CI]	*P*-value (Two-sided)	Significance level (Two-sided)
	Eribulin mesilate	DTIC	Overall			
Interim analysis	[redacted]	[redacted]	247	[redacted] [redacted]	[redacted]	0.0139
Dry Run 1	138	155	293	0.756 [0.596, 0.959]	0.0208	0.0226
Dry Run 2	149	163	312	0.744 [0.591, 0.936]	0.0114	0.0240
Dry Run 3	161	171	332	0.759 [0.607, 0.949]	0.0152	0.0290
Dry Run 4	171	177	348	0.759 [0.610, 0.946]	0.0137	0.0312
Dry Run 5	174	180	354	0.761 [0.612, 0.946]	0.0137	0.0296
Dry Run 6	176	181	357	0.757 [0.609, 0.940]	0.0116	0.0298
Final analysis	176	181	357	0.768 [0.618, 0.954]	0.0169	0.0303

PMDA's view:

Given the OS by DTIC dose level selected before randomization in Foreign Study E7389-G000-309, all subjects receiving DTIC at different doses can be combined into the single DTIC group, to be compared with the eribulin mesilate group. The eribulin mesilate group achieved longer OS than the single DTIC group; this finding demonstrates the efficacy of eribulin mesilate in the target patient population of the study.

3.(ii).C.(1).3) Efficacy in Japanese patients

The applicant explained that the following findings also support the efficacy of eribulin mesilate in the treatment of Japanese patients:

- The PFR_{12wks} [two-sided 90% CI] in patients with liposarcoma or leiomyosarcoma in Japanese Study E7389-J081-217 was 60.0% [44.7%, 74.0%], and the lower limit of the two-sided 90% CI was higher than the pre-specified threshold (20%). Furthermore, the study showed good PFR_{12wks} values.
- In Japanese Study E7389-J081-217, the median OS [95% CI] in patients with liposarcoma or leiomyosarcoma was 17.0 [11.0, 20.5] months. In Foreign Study E7389-G000-309, the median OS [95% CI] in the eribulin mesilate group was 13.5 [10.9, 15.6] months. In Foreign Study E7389-E044-207, the median OS [95% CI] in pooled data from patients with liposarcoma and those with leiomyosarcoma was 14.0 [10.7, 16.5] months. Although a comparison of these different studies has limitations, the OS in Japanese Study E7389-J081-217 was not inferior to that in Foreign Study E7389-G000-309 or Foreign Study E7389-E044-207.

PMDA's view:

Because Japanese Study E7389-J081-217 was an open-label uncontrolled study, PFR_{12wks}-based evaluation of the efficacy of eribulin mesilate has limitations. Nevertheless, the applicant's explanation is acceptable.

3.(ii).C.(2) Safety

PMDA's conclusion on the safety profile of eribulin mesilate after discussion [for discussion summary, see "3.(ii).C.(2).1)" to "3.(ii).C.(2).3)"]:

When treating patients with STS with eribulin mesilate, special attention should be paid to QT/QTc prolongation as well as to the adverse events identified as requiring attention prior to the initial approval for the indication of breast cancer (i.e., bone marrow depression, peripheral nerve disorder, infections, hepatic function disorder, and interstitial lung disease) (see the "Review Report on Halaven Injection 1 mg dated January 12, 2011"). Eribulin mesilate is tolerable in patients with STS as long as they are followed by a physician with sufficient knowledge and experience in cancer chemotherapy, through dose reduction or suspension or discontinuation of the drug as appropriate.

3.(ii).C.(2).1) Differences in the safety profile of eribulin mesilate between Japanese and non-Japanese patients

The applicant's explanation on the safety profile of eribulin mesilate in patients with unresectable STS, based on the safety data obtained from Japanese Study E7389-J081-217 and Foreign Study E7389-G000-309:

The safety results from the 2 studies are summarized in the table below.

Safety summary (Japanese Study E7389-J081-217 and Foreign Study E7389-G000-309)

	n (%)		
	Japanese Study E7389-J081-217	Foreign Study E7389-G000-309	
	N = 51	Eribulin mesilate N = 226	DTIC N = 224
All adverse events	51 (100)	224 (99.1)	218 (97.3)
Grade ≥3 adverse events	49 (96.1)	152 (67.3)	126 (56.3)
Adverse events resulting in death	1 (2.0)	10 (4.4)	3 (1.3)
Serious adverse events	15 (29.4)	76 (33.6)	71 (31.7)
Adverse events leading to treatment discontinuation	4 (7.8)	17 (7.5)	11 (4.9)
Adverse events leading to dose reduction, delay, or suspension	16 (31.4)	99 (43.8)	82 (36.6)

In Foreign Study E7389-G000-309, the following adverse events occurred in the eribulin mesilate group at a ≥10% higher incidence than in the DTIC group: neutropenia (99 of 226 subjects [43.8%] in the eribulin mesilate group, 53 of 224 subjects [23.7%] in the DTIC group), alopecia (79 of 226 subjects [35.0%], 6 of 224 subjects [2.7%]), pyrexia (63 of 226 subjects [27.9%], 31 of 224 subjects [13.8%]), and peripheral sensory neuropathy (46 of 226 subjects [20.4%], 8 of 224 subjects [3.6%]). The following Grade ≥3 adverse events occurred in the eribulin mesilate group at a ≥3% higher incidence than in the DTIC group: neutropenia (80 of 226 subjects [35.4%], 35 of 224 subjects [15.6%]), leukopenia (23 of 226 subjects [10.2%], 10 of 224 subjects [4.5%]), and neutrophil count decreased (16 of 226 subjects [7.1%], 6 of 224 subjects [2.7%]). The following serious adverse event occurred in the eribulin mesilate group at a ≥2% higher incidence than in the DTIC group: pyrexia (10 of 226 subjects [4.4%], 4 of 224 subjects [1.8%]). There were no adverse events leading to treatment discontinuation reported in the eribulin mesilate group at a ≥2% higher incidence than in the DTIC group. The following adverse events led to dose reduction, delay, or suspension, occurring in the eribulin mesilate group at a ≥2% higher incidence than in the DTIC group: neutropenia (48 of 226 subjects [21.2%], 30 of 224 subjects [13.4%]),

peripheral sensory neuropathy (9 of 226 subjects [4.0%], 0 subjects), and pyrexia (7 of 226 subjects [3.1%], 1 of 224 subjects [0.4%]).

The safety profile of eribulin mesilate in Japanese patients (Japanese Study E7389-J081-217) was compared with that in non-Japanese patients (Foreign Study E7389-G000-309). The table below shows the adverse events with a ≥10% difference in incidence between the 2 studies.

Adverse events with a ≥10% difference in incidence between Japanese Study E7389-J081-217 and Foreign Study E7389-G000-309

Preferred Term (MedDRA/J Ver.17.1)	n (%)			
	Japanese		Non-Japanese	
	Japanese Study E7389-J081-217 N = 51		Foreign Study E7389-G000-309 (Eribulin mesilate group) N = 226	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	51 (100)	49 (96.1)	224 (99.1)	152 (67.3)
Leukopenia	51 (100)	38 (74.5)	36 (15.9)	23 (10.2)
Neutropenia	50 (98.0)	44 (86.3)	99 (43.8)	80 (35.4)
Lymphopenia	40 (78.4)	17 (33.3)	3 (1.3)	3 (1.3)
Anaemia	24 (47.1)	7 (13.7)	67 (29.6)	16 (7.1)
Cancer pain	23 (45.1)	3 (5.9)	4 (1.8)	2 (0.9)
Pyrexia	21 (41.2)	1 (2.0)	63 (27.9)	2 (0.9)
Malaise	20 (39.2)	0	2 (0.9)	0
Neuropathy peripheral	16 (31.4)	0	1 (0.4)	0
Alanine aminotransferase increased	14 (27.5)	3 (5.9)	18 (8.0)	3 (1.3)
Aspartate aminotransferase increased	13 (25.5)	2 (3.9)	21 (9.3)	1 (0.4)
Stomatitis	13 (25.5)	0	31 (13.7)	2 (0.9)
Dysgeusia	12 (23.5)	0	18 (8.0)	0
Blood lactate dehydrogenase increased	11 (21.6)	0	12 (5.3)	0
Nasopharyngitis	11 (21.6)	0	8 (3.5)	0
Upper respiratory tract infection	11 (21.6)	0	20 (8.8)	1 (0.4)
Hypoalbuminaemia	10 (19.6)	2 (3.9)	11 (4.9)	2 (0.9)
Fatigue	9 (17.6)	0	99 (43.8)	7 (3.1)
Hypophosphataemia	8 (15.7)	5 (9.8)	6 (2.7)	2 (0.9)
Blood creatine phosphokinase increased*	8 (15.7)	0	–	–
C-reactive protein increased*	6 (11.8)	0	–	–
Vomiting	4 (7.8)	0	43 (19.0)	2 (0.9)
Peripheral sensory neuropathy	3 (5.9)	0	46 (20.4)	4 (1.8)
Dyspnoea	3 (5.9)	1 (2.0)	36 (15.9)	5 (2.2)
Abdominal pain	1 (2.0)	0	45 (19.9)	4 (1.8)
Asthenia	0	0	47 (20.8)	4 (1.8)

* C-reactive protein was not measured in Foreign Study E7389-G000-309.

The serious adverse events reported in ≥1 Japanese subject at a ≥2% higher incidence than in non-Japanese subjects were cancer pain (3 of 51 Japanese subjects [5.9%], 2 of 226 non-Japanese subjects [0.9%]) and ileus (2 of 51 Japanese subjects [3.9%], 1 of 226 non-Japanese subjects [0.4%]). The adverse event leading to dose reduction, delay, or suspension reported in Japanese subjects at a ≥2% higher incidence than in non-Japanese subjects was neutropenia (13 of 51 Japanese subjects [25.5%], 48 of 226 non-Japanese subjects [21.2%]). There were no adverse events leading to treatment discontinuation reported in ≥1 Japanese subject at a ≥2% higher incidence than in non-Japanese subjects.

The following adverse events occurred in ≥1 Japanese subject but in no non-Japanese subjects: blood creatine phosphokinase* increased in 8 of 51 subjects (15.7%), C-reactive protein* increased in 6 of 51

subjects (11.8%), hepatic function abnormal and hypertriglyceridaemia* in 5 of 51 subjects (9.8%) each, cheilitis, gingivitis, hypoproteinaemia, and osteoarthritis in 3 of 51 subjects (5.9%) each, and injection site extravasation, foot fracture, blood urine present, protein urine, and oropharyngeal discomfort in 2 of 51 subjects (3.9%) each. All events were Grade 1 or 2 except for Grade 3 hypertriglyceridaemia in 1 subject.

* Neither blood creatine phosphokinase nor C-reactive protein was measured in Foreign Study E7389-G000-309.

PMDA's discussion:

The adverse events reported more frequently in the eribulin mesilate group than in the DTIC group in Foreign Study E7389-G000-309 require special attention during treatment with eribulin mesilate in patients with STS. The occurrence of the events should be appropriately communicated to healthcare professionals using suitable materials. There are some difficulties in a comparison of the safety profile of eribulin mesilate between Japanese and non-Japanese patients with STS due to limited use experience of eribulin mesilate in Japanese patients. Nevertheless, particular attention should be paid to Grade ≥3 adverse events (e.g., bone marrow depression) that occurred more frequently in Japanese subjects than in non-Japanese subjects.

3.(ii).C.(2).2) Differences in the safety profile of eribulin mesilate between patients with STS and patients with breast cancer

The applicant made a comparison of the safety profile of eribulin mesilate between Japanese patients with STS (Japanese Phase II Study E7389-J081-217) and those with breast cancer (Japanese Phase II Study E7389-A001-221, including the extension study E7389-J081-224), and between non-Japanese patients with STS (Foreign Phase III Study E7389-G000-309) and those with breast cancer (Foreign Phase III Study E7389-G000-305).

The applicant's explanation on differences in the safety profile between patients with STS and those with breast cancer:

The safety results from the respective studies are summarized in the table below.

Summary of safety results in patients with STS and patients with breast cancer

	n (%)			
	Japanese phase II studies		Foreign phase III studies	
	Patients with STS Study E7389-J081-217 N = 51	Patients with breast cancer Study E7389-A001-221*1 N = 81	Patients with STS Study E7389-G000-309 N = 226	Patients with breast cancer Study E7389-G000-305 N = 503
All adverse events	51 (100)	81 (100)	224 (99.1)	497 (98.8)
Grade ≥3 adverse events	49 (96.1)	78 (96.3)	152 (67.3)	352 (70.0)
Adverse events resulting in death	1 (2.0)	0	10 (4.4)	18 (3.6)
Serious adverse events	15 (29.4)	14 (17.3)	76 (33.6)	130 (25.8)
Adverse events leading to treatment discontinuation	4 (7.8)	6 (7.4)	17 (7.5)	71 (14.1)
Adverse events leading to dose reduction, delay, or suspension*2	16 (31.4)	–	99 (43.8)	234 (46.5)

*1 Including data from Japanese Study E7389-J081-224, the extension study to Japanese Study E7389-A001-221;

*2 Japanese Study E7389-A001-221 did not collect data on dose reduction, delay, or suspension of eribulin mesilate. (It collected data on discontinuation only.)

In Japanese phase II studies, the following adverse events occurred in subjects with STS at an ≥10% higher incidence than in subjects with breast cancer: lymphopenia (40 of 51 subjects with STS [78.4%], 34 of 81 subjects with breast cancer [42.0%]), anaemia (24 of 51 subjects [47.1%], 7 of 81 subjects [8.6%]), cancer pain (23 of 51 subjects [45.1%], 3 of 81 subjects [3.7%]), pyrexia (21 of 51 subjects [41.2%], 25 of 81 subjects [30.9%]), malaise (20 of 51 subjects [39.2%], 12 of 81 subjects [14.8%]), constipation (16 of 51 subjects [31.4%], 14 of 81 subjects [17.3%]), neuropathy peripheral (16 of 51 subjects [31.4%], 2 of 81 subjects [2.5%]), upper respiratory tract infection (11 of 51 subjects [21.6%], 0 subjects), hypoalbuminaemia (10 of 51 subjects [19.6%], 1 of 81 subjects [1.2%]), and hypophosphataemia (8 of 51 subjects [15.7%], 3 of 81 subjects [3.7%]). The following Grade ≥3 adverse events occurred in subjects with STS at a ≥3% higher incidence than in subjects with breast cancer: lymphopenia (17 of 51 subjects [33.3%], 10 of 81 subjects [12.3%]), anaemia (7 of 51 subjects [13.7%], 0 subjects), hypophosphataemia (5 of 51 subjects [9.8%], 1 of 81 subjects [1.2%]), hypokalaemia (3 of 51 subjects [5.9%], 1 of 81 subjects [1.2%]), cancer pain (3 of 51 subjects [5.9%], 1 of 81 subjects [1.2%]), and hypoalbuminaemia (2 of 51 subjects [3.9%], 0 subjects).

In foreign phase III studies, the following adverse events occurred in subjects with STS at a ≥10% higher incidence than in subjects with breast cancer: fatigue (99 of 226 subjects (43.8%), 148 of 503 subjects [29.4%]), anaemia (67 of 226 subjects [29.6%], 97 of 503 subjects [19.3%]), and abdominal pain (45 of 226 subjects [19.9%], 38 of 503 subjects [7.6%]). The following Grade ≥3 adverse events occurred in subjects with STS at a ≥3% higher incidence than in subjects with breast cancer: anaemia (16 of 226 subjects [7.1%], 10 of 503 subjects [2.0%]) and neutrophil count decreased (16 of 226 subjects [7.1%], 5 of 503 subjects [1.0%]).

In either comparison, the incidence of anaemia in subjects with STS was higher by ≥10% than that in subjects with breast cancer, and the incidence of Grade ≥3 anaemia in subjects with STS was higher by ≥5% than that in subjects with breast cancer. However, adverse events observed in subjects with STS were similar to those observed in subjects with breast cancer, showing no clear difference in the safety profile of eribulin mesilate between these 2 patient populations.

PMDA's discussion:
The adverse events observed during treatment with eribulin mesilate in Japanese Study E7389-J081-217 and Foreign Study E7389-G000-309 were similar to those in patients with breast cancer, the approved indication of eribulin mesilate. There were no clear differences in the incidence of adverse events resulting in death or leading to treatment discontinuation between the 2 patient populations. Therefore, eribulin mesilate is also tolerable in patients with STS as long as they are followed appropriately, through monitoring and controlling of adverse events, by a physician with sufficient knowledge and experience in cancer chemotherapy with a good understanding of the safety profile of eribulin mesilate in these patients. However, some adverse events, including anaemia, occurred more frequently in patients with

STS than in patients with breast cancer; the incidences of these adverse events should be appropriately communicated to healthcare professionals using suitable materials.

At the initial approval, PMDA concluded that the occurrence of QT/QTc prolongation in a foreign clinical pharmacology study (Foreign Study E7389-E044-110) should be communicated to healthcare professionals using suitable materials (see the "Review Report on Halaven Injection 1 mg dated January 12, 2011"). The following section is a summary of review by PMDA on the safety of eribulin mesilate with a focus on QT/QTc prolongation.

3.(ii).C.(2).3) QT/QTc prolongation

The applicant's explanation on QT/QTc prolongation during treatment with eribulin mesilate:

The protocols of Japanese Study E7389-J081-217 and Foreign Study E7389-G000-309 required electrocardiogram (ECG) on a regular basis. In Foreign Study E7389-E044-207, ECG was performed but no data of ECG parameters were collected.

Adverse events related to QT/QTc prolongation (MedDRA preferred terms categorized into "torsade de pointes/QT prolongation" in the Standard MedDRA Queries [MedDRA/J ver.17.1]) were collected and analyzed.

In Japanese Study E7389-J081-217, QT/QTc prolongation occurred in 1 of 51 subjects (2.0%). The event was a non-serious Grade 2 electrocardiogram QT prolonged, which eventually resolved with no change in the treatment regimen of eribulin mesilate.

In Foreign Study E7389-G000-309, QT/QTc prolongation occurred in 15 of 226 subjects (6.6%) in the eribulin mesilate group and 11 of 224 subjects (4.9%) in the DTIC group. Grade ≥3 QT/QTc prolongation occurred in 5 of 226 subjects (2.2%) in the eribulin mesilate group and 3 of 224 subjects (1.3%) in the DTIC group. All the relevant events were electrocardiogram QT prolonged. In the eribulin mesilate group, serious QT/QTc prolongation occurred in 1 of 226 subjects (0.4%), QT/QTc prolongation leading to treatment discontinuation occurred in 1 of 226 subjects (0.4%). QT/QTc prolongation leading to dose reduction, delay, or suspension occurred in 1 of 226 subjects (0.4%) in the eribulin mesilate group and 1 of 224 subjects (0.4%) in the DTIC group. The outcomes of electrocardiogram QT prolonged in the eribulin mesilate group were "resolved" or "resolving" in all subjects except for 4 subjects ("not resolved" in 3 subjects, "outcome unknown" in 1 subject).

In Foreign Study E7389-E044-207, QT/QTc prolongation was not observed in any subject.

The table below presents the changes in QTcF in subjects in Japanese Study E7389-J081-217 and in the eribulin mesilate group in Foreign Study E7389-G000-309. In both studies, all the subjects experiencing a QTcF >500 msec after administration or a >60 msec increase from baseline in QTcF eventually recovered from these events without modifying the treatment regimen (discontinuation, dose reduction,

delay, or suspension of eribulin mesilate). The subjects experiencing changes in QTcF had electrolyte abnormality (hypokalaemia or hypomagnesaemia), adverse events suspected to be related to QT/QTc prolongation (nausea, vomiting, diarrhoea, or inappetence), prior treatment with DXR, and the concomitant use of a drug with a QTc prolongation effect. These factors may have contributed to the occurrence of QT/QTc prolongation after the administration of eribulin mesilate:

Changes in QTcF intervals after the administration of eribulin mesilate (Japanese Study E7389-J081-217 and the eribulin mesilate group in Foreign Study E7389-G000-309)

	n (%)		
	Japanese Study E7389-J081-217	Foreign Study E7389-G000-309	
	QTcF N = 51	QTcF N = 110	QTcF Derived* N = 226
Max			
>500 msec	2 (3.9)	2 (1.8)	9 (4.0)
>550 msec	0	0	0
Increase from baseline			
>60 msec	3 (5.9)	7 (6.4)	13 (5.8)
>100 msec	1 (2.0)	0	4 (1.8)
Mean increase from baseline and mean absolute value [95% CI] (msec)			
Increased value	5.5 [2.0, 8.9]	4.3 [1.5, 7.0]	4.1 [2.0, 6.1]
Absolute value	419.1 [413.9, 424.3]	420.5 [416.8, 424.1]	422.6 [419.8, 425.4]

* In Foreign Study E7389-G000-309, either QTcF or QT interval corrected using the Bazett's formula (QTcB) was measured. The results of QTcF Derived were therefore calculated based on RR interval or heart rate and QT interval, or QTcB.

Post-marketing safety data (data cut-off on October 16, 2015) showed electrocardiogram QT prolonged (categorized as QT/QTc prolongation) in 1 Japanese patient and 3 non-Japanese patients. The events were serious in the Japanese patient and 2 of the 3 non-Japanese patients.

PMDA's discussion:

Prior to the initial approval, QT/QTc prolongation was identified in patients with advanced solid tumors in Foreign Study E7389-E044-110. At the initial approval, PMDA advised the applicant to provide appropriate information regarding the risk of QT/QTc prolongation to healthcare professionals through written materials, concluding that other preventive measures were unnecessary because (1) Foreign Study E7389-E044-110 did not show any relationship between plasma eribulin concentrations and QTcF prolongation, and (2) nonclinical safety pharmacology studies showed no effects of eribulin mesilate on the QT/QTc interval.

In Foreign Study E7389-G000-309, the eribulin mesilate group had no clear tendency toward a higher incidence of QT/QTc prolongation than the DTIC group. Nevertheless, Grade ≥3 QT/QTc prolongation occurred in the eribulin mesilate group, leading to the discontinuation of treatment in some subjects. This indicates need for attention to prolonged QT/QTc during eribulin mesilate therapy. Therefore the package insert and other written materials should advise healthcare professionals to monitor patients by regular follow-up and ECG, etc. and to take appropriate actions upon the detection of the event. The currently available data on QT/QTc prolongation observed during treatment with eribulin mesilate suggest the possible contribution of factors other than eribulin mesilate to the events; the data also showed that prolongation was transient in many patients. Therefore information on QT/QTc

prolongation should be further collected and examined. Currently available findings on QT/QTc prolongation should be communicated to healthcare professionals appropriately through suitable materials.

3.(ii).C.(3) Clinical positioning and indications

The proposed indication for eribulin mesilate was "soft tissue sarcoma." The proposed "Precautions for Indication" section of the package insert were as follows:

- The efficacy and safety of eribulin mesilate in chemotherapy-naïve patients have not been established.
- Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, including histological types of STS in patients enrolled in the clinical studies, and based on adequate knowledge of the efficacy and safety of eribulin mesilate.

PMDA's conclusion after discussion [for discussion summary, see "3.(ii).C.(1) Efficacy," "3.(ii).C.(2) Safety," and "3.(ii).C.(3).1)" to"3.(ii).C.(3).3)"]:

The proposed indication for eribulin mesilate "soft tissue sarcoma" is appropriate. The precautionary advice proposed by the applicant should be added in the "Precautions for Indication" section. Information, such as histological types of STS of patients enrolled in the clinical studies, should be provided in the "Clinical Studies" section of the package insert.

3.(ii).C.(3).1) Clinical positioning of eribulin mesilate

In major foreign clinical practice guidelines in oncology, eribulin mesilate is mentioned as a treatment option for patients with unresectable STS (see below). Meanwhile, none of the following guidelines/textbooks mention eribulin mesilate as a therapeutic drug for unresectable STS: the US National Cancer Institute Physician Data Query (NCI-PDQ); Adult Soft Tissue Sarcoma Treatment (June-2-2015 version); ESMO Guidelines 2014 version (*Ann Oncol*. 2014;25(suppl 3):iii102-iii112); the Clinical Practice Guidelines for Soft Tissue Sarcoma 2012 supervised by the Japanese Orthopaedic Association (Nankodo. 2012); DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition (Lippincott Williams & Wilkins. 2014. USA), a major textbook of clinical oncology used in and outside Japan; or the New Clinical Oncology Fourth Revision edited by the Japanese Society of Medical Oncology (Nankodo. 2015).

Clinical practice guidelines

- The NCCN guidelines (v.1.2015): Eribulin mesilate is a therapeutic option recommended for STS of non-specific histological types.

The applicant's explanation on the clinical positioning of eribulin mesilate:

Outside Japan, before the beginning of Study E7389-G000-309, epirubicin hydrochloride (an anthracycline) was available for the treatment of unresectable STS in addition to the standard therapy with DXR, and there were several therapeutic options for patients previously treated with chemotherapy

including DXR. Foreign Study E7389-G000-309 therefore enrolled patients with STS previously treated with ≥2 chemotherapy regimens including ≥1 regimen with an anthracycline. The applicant considers that patients with STS previously treated with chemotherapy such as DXR are eligible for eribulin mesilate therapy irrespective of the number of previous chemotherapy regimens, for the following reasons: (1) Foreign Study E7389-G000-309 demonstrated the clinical benefits of eribulin mesilate; (2) Before the beginning of the study, no drugs had been proven by a controlled clinical study to be effective or safe in patients with unresectable STS previously treated with DXR or other chemotherapy. Thus, eribulin mesilate is a viable therapeutic option for patients with unresectable STS previously treated with DXR or other chemotherapy.

Pazopanib hydrochloride (pazopanib) and trabectedin have been approved for the treatment of patients with unresectable STS previously treated with DXR or other chemotherapy. PMDA asked the applicant to explain when to use pazopanib or trabectedin and when to use eribulin mesilate.

The applicant's response:
The safety profile of eribulin mesilate is different from that of pazopanib or trabectedin. The histological types of STS evaluated in clinical studies of eribulin mesilate also differ from those evaluated in clinical studies of pazopanib or trabectedin. In clinical settings, an appropriate drug is expected to be selected according to the safety profiles and the histological types of STS evaluated in the clinical studies.

PMDA accepted the applicant's explanation.

3.(ii).C.(3).2) Target histological types and indication of eribulin mesilate
The applicant's explanation on how target histological types were determined for Foreign Study E7389-G000-309 and Japanese Study E7389-J081-217:
In Foreign Study E7389-E044-207 in patients with unresectable STS of high or intermediate malignancy, STS was stratified into the following histological types according to the WHO classification of STS (2002).

- Liposarcoma (dedifferentiated, myxoid or round cell, pleomorphic, or mixed-type not otherwise specified)
- Leiomyosarcoma
- Synovial sarcoma
- Other histological types

Foreign Study E7389-E044-207 used Simon's 2-stage design (optimal method) with a threshold PFR_{12wks} of 20%, expectation of 40%, one-sided significance level of 10%, and a statistical power of 90%. In Stage 1, 17 subjects each were enrolled for liposarcoma, leiomyosarcoma, synovial sarcoma, and other histological types. When ≥4 subjects achieved progression free survival, Stage 2 began. In Stage 2, up to 37 additional subjects were enrolled, and eribulin mesilate was considered effective when

≥11 subjects achieved progression free survival. When ≤3 subjects achieved progression free survival, no further evaluation was performed.

Foreign Study E7389-E044-207 showed favorable results in patients with liposarcoma or leiomyosarcoma. Foreign Study E7389-G000-309 was therefore designed to enroll these patient populations [see "3.(ii).B.(2).1) Foreign phase II study"].

Japanese Study E7389-J081-217 enrolled patients with STS of the same histological types as in Foreign Study E7389-E044-207, and these patients were stratified into 2 groups: "liposarcoma or leiomyosarcoma" (target patients in Foreign Study E7389-G000-309) and "other histological types."

Japanese Study 217 and Foreign Study E7389-E044-207 excluded patients with STS of any of the histological types shown in the table below.

Histological types ineligible for Japanese Study E7389-J081-217 or Foreign Study E7389-E044-207 and reasons for ineligibility

Histological type	Reason for ineligibility
Embryonal rhabdomyosarcoma	It is classified as STS but ineligible because it develops mainly in pediatric or juvenile patients. Recommended therapies are combination therapies with vincristine sulfate, actinomycin, and cyclophosphamide hydrate, etc.
Chondrosarcoma Osteosarcoma Ewing's sarcoma/PNET	In most patients, these sarcomas are classified as bone tumors, not as STS.
Gastrointestinal stromal tumor	It is classified as STS but ineligible because it requires a different therapeutic approach. Recommended therapeutic agents include imatinib mesilate, sunitinib malate, or regorafenib hydrate.
Dermatofibrosarcoma protuberans	It is classified as STS but ineligible because it requires a partially different therapeutic approach. Imatinib mesilate is recommended in foreign countries.
Inflammatory myofibroblastic tumor	It is classified as STS but ineligible because it develops mainly in pediatric or juvenile patients. Approximately half of the patients have ALK gene mutation (chromosomal translocation). Outside Japan, crizotinib is recommended for patients with ALK gene mutation.
Neuroblastoma	Approximately 90% of patients are <5 years old. Neuroblastoma is classified as childhood cancer, not as STS developing in adults.
Malignant mesothelioma	It is classified as mesothelioma, not as STS.
Uterine mixed mesodermal tumor	It is classified as uterine cancer, not as STS.

ALK, anaplastic lymphoma kinase

In light of the target patient populations of the clinical studies, the applicant plans to include the following precautionary statements in the "Clinical Studies" section of the package insert: (a) Foreign Study E7389-G000-309 enrolled patients with liposarcoma or leiomyosarcoma. (b) Japanese Study E7389-J081-217 excluded patients with tumors of any of the histological types shown in the table above (the "Clinical Studies" section). The applicant also plans to ensure that the "Precautions for Indications" section includes precautionary advice regarding the histological types of STS in the patients enrolled in the clinical studies.

PMDA asked the applicant to explain (a) the histological types of STS eligible for Japanese Study E7389-J081-217 and Foreign Study E7389-E044-207, other than liposarcoma and leiomyosarcoma (the

target histological types in Foreign Study E7389-G000-309) and (b) the clinical benefits of eribulin mesilate for any histological types excluded from Studies E7389-J081-217 and E7389-E044-207.

The applicant's response:

(a) Histological types of STS that were excluded from Foreign Study E7389-G000-309 but were included in Japanese Study E7389-J081-217 or Foreign Study E7389-E044-207:

Because of a limited number of subjects, there were limitations to the evaluation of efficacy of eribulin mesilate in individual histological types. The table below is a summary of best overall responses in patients with STS of various histological types, except for liposarcoma and leiomyosarcoma, who received eribulin mesilate in Japanese Study E7389-J081-217 or Foreign Study E7389-E044-207.

Best overall responses by histological type of STS
(Japanese Study E7389-J081-217[*1] and Foreign Study E7389-E044-207[*2])

Histological type	Japanese Study E7389-J081-217					Foreign Study E7389-E044-207				
	n	Best overall response				n	Best overall response			
		CR	PR	SD	PD		CR	PR	SD	PD
Synovial sarcoma	3	0	0	2	1	19	0	1	8	10
Adult fibrosarcoma	1	0	0	0	1	0	0	0	0	0
Myxofibrosarcoma	1	0	0	1	0	0	0	0	0	0
Sclerosing epithelioid fibrosarcoma	0	0	0	0	0	2	0	0	2	0
Solitary fibrous tumor	2	0	0	1	1	1	0	0	1	0
Pleomorphic malignant fibrous histiocytoma	3	0	0	0	3	2	0	0	0	2
Alveolar rhabdomyosarcoma	1	0	0	0	1	0	0	0	0	0
Rhabdomyosarcoma (subtype unknown)	1	0	0	0	1	1	0	0	1	0
Angiosarcoma of soft tissue	0	0	0	0	0	2	0	0	1	1
Epithelioid sarcoma	0	0	0	0	0	4	0	1	2	1
Alveolar soft part sarcoma	1	0	0	1	0	2	0	0	1	1
Clear cell sarcoma	0	0	0	0	0	1	0	0	0	1
Malignant peripheral nerve sheath tumor	1	0	0	1	0	1	0	0	1	0
Unclassified, undifferentiated soft tissue sarcoma	0	0	0	0	0	8	0	0	2	6
Other sarcoma	2	0	0	2	0	2	0	0	0	2

[*1] FAS, independent review of images, RECIST ver.1.1;
[*2] Efficacy analysis population, investigator's assessment, RECIST ver.1.0;
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

The table below is a summary of safety results from Japanese Study E7389-J081-217 and Foreign Study E7389-E044-207 by histological type-based subgroup. There were no clear differences in the safety profile of eribulin mesilate by histological type including liposarcoma and leiomyosarcoma, the target histological types of STS in Foreign Study E7389-G000-309.

Summary of safety results by histological type-based subgroup
(Japanese Study E7389-J081-217 and Foreign Study E7389-E044-207)

	n (%)					
	Japanese Study E7389-J081-217		Foreign Study E7389-E044-207			
	Liposarcoma or leiomyosarcoma N = 35	Other histological types N = 16	Liposarcoma N = 37	Leiomyosarcoma N = 40	Synovial sarcoma N = 19	Other histological types N = 31
All adverse events	35 (100)	16 (100)	36 (97.3)	38 (95.0)	19 (100)	31 (100)
Grade ≥3 adverse events	33 (94.3)	16 (100)	20 (54.1)	19 (47.5)	9 (47.4)	18 (58.1)
Adverse events resulting in death	1 (2.9)	0	1 (2.7)	2 (5.0)	0	0
Serious adverse events	10 (28.6)	5 (31.3)	14 (37.8)	12 (30.0)	7 (36.8)	14 (45.2)

	n (%)					
	Japanese Study E7389-J081-217		Foreign Study E7389-E044-207			
	Liposarcoma or leiomyosarcoma N = 35	Other histological types N = 16	Liposarcoma N = 37	Leiomyosarcoma N = 40	Synovial sarcoma N = 19	Other histological types N = 31
Adverse events leading to treatment discontinuation*	2 (5.7)	2 (12.5)	3 (8.1)	3 (7.5)	2 (10.5)	3 (9.7)
Adverse events leading to dose reduction, delay, or suspension*	12 (34.3)	4 (25.0)	–	–	–	–

* In Foreign Study E7389-E044-207, data on actions taken with eribulin mesilate were not collected. The figures in "Adverse events leading to treatment discontinuation" represent the number of subjects who discontinued treatment primarily due to an adverse event.

In Japanese Study E7389-J081-217 and Foreign Study E7389-E044-207, patients with STS of the following histological types were eligible for enrollment, but none of these patients received eribulin mesilate: low grade fibromyxoid sarcoma, giant cell malignant fibrous histiocytoma, inflammatory malignant fibrous histiocytoma, malignant glomus tumor, pleomorphic rhabdomyosarcoma, epithelioid hemangioendothelioma, desmoplastic small round cell tumor, extra-renal rhabdoid tumor, malignant mesenchymoma, perivascular epithelioid cell tumor, and intimal sarcoma.

STS is an extremely rare disease developing in various soft tissues of the body and is classified into more than 50 histological types. Evaluating the efficacy of eribulin mesilate against each histological type is difficult in light of the feasibility of clinical trials. Nevertheless, eribulin mesilate is expected be clinically beneficial in patients with STS of the histological types evaluated in Japanese Study E7389-J081-217 or Foreign Study E7389-E044-207, for the following reasons:

- In both studies, all subjects with STS of any target histological types, including liposarcoma and leiomyosarcoma, were treated with the same therapeutic approach.
- In both studies, some subjects with STS of the target histological types responded to eribulin mesilate. There were no clear differences in the safety profile of eribulin mesilate among the histological types including liposarcoma and leiomyosarcoma.

(b) Histological types that were excluded from Japanese Study E7389-J081-217 or Foreign Study E7389-E044-207:

The following histological types were excluded from Japanese Study E7389-J081-217 or Foreign Study E7389-E044-207 and clinical benefits of eribulin mesilate for patients with these histological types remain unknown: embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing's sarcoma/primitive neuroectodermal tumor, gastrointestinal stromal tumor, dermatofibrosarcoma protuberans, inflammatory myofibroblastic tumor, neuroblastoma, malignant mesothelioma, and uterine mixed mesodermal tumor.

PMDA's discussion:

Patients with liposarcoma or leiomyosarcoma were enrolled in Foreign Study E7389-G000-309. Eribulin mesilate should therefore be recommended for the treatment of these tumors. The applicant explained that it was difficult to evaluate the efficacy of eribulin mesilate for all individual histological

types. This explanation is understandable to some extent because of the diverse histological types and the rareness of STS. The histological types presented in (a) should not necessarily be excluded from the indications of eribulin mesilate, in view of the applicant's explanation and the extremely limited therapeutic options for these histological types. However, the histological types mentioned in (b) should be excluded from the indications of eribulin mesilate because of unproven clinical benefits for these histological types. Nevertheless, eribulin mesilate is expected to be administered by physicians with sufficient knowledge and experience in chemotherapy for STS. Therefore, eligible patients for the therapy will be selected properly by the physicians, provided that they are appropriately informed of the results of Foreign Study E7389-G000-309, Japanese Study E7389-J081-217, and Foreign Study E7389-E044-207 and the target patient populations of these studies.

Accordingly, PMDA concluded that the proposed indication of eribulin mesilate of "soft tissue sarcoma," including that of rare histological types, is acceptable. However, the "Clinical Studies" section of the package insert, etc. should mention (a) the histological types excluded from the clinical studies and (b) the efficacy of eribulin mesilate against individual histological types evaluated in the clinical studies, in order to appropriately raise awareness among healthcare professionals. The following precautionary advice should also be given in the "Precautions for Indications" section:

- Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, including histological types of STS in patients enrolled in the clinical studies, and based on adequate knowledge of the efficacy and safety of eribulin mesilate.

3.(ii).C.(3).3) Previous treatment

The applicant's explanation on the use of eribulin mesilate in chemotherapy-naïve patients:

In and outside Japan, DXR has been used as the established standard therapy for patients with unresectable STS, and no clinical studies have been conducted in chemotherapy-naïve patients to evaluate the efficacy and safety of eribulin mesilate. The efficacy and safety of eribulin mesilate therefore have not been established in chemotherapy-naïve patients; this information will be highlighted in the "Precautions for Indications" section of the package insert.

PMDA accepted the applicant's explanation.

3.(ii).C.(4) Dosage and administration

The proposed dosage and administration is 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 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." This is identical to the approved dosage and administration for breast cancer. The proposed content of "Precautions for Dosage and Administration" is shown below. This is also identical to that for breast cancer, the approved indication.

- The efficacy and safety of eribulin mesilate in combination with other antitumor drugs have not been established.

- Criteria for the start of treatment in case of an adverse drug reaction in the previous cycle, and criteria for dose reduction, resumption, and suspension of eribulin mesilate in case of an adverse drug reaction
- Dose reduction should be considered for patients with hepatic impairment.
- Japanese pharmacopoeia physiological saline should be used to dilute eribulin mesilate.

PMDA's conclusion after discussion [for discussion summary, see "3.(ii).C.(1) Efficacy," "3.(ii).C.(2) Safety," and "3.(ii).C.(4).1)" to "3.(ii).C.(4).4)"]:
The proposed dosage and administration of eribulin mesilate is appropriate. The "Precautions for Dosage and Administration" section of the package insert should give the same precautionary advice as for the approved indication.

3.(ii).C.(4).1) Dosage and administration of eribulin mesilate

The applicant's rationale for the proposed dosage and administration of eribulin mesilate:
The proposed dosage and administration of eribulin mesilate for STS is the same as the approved dosage for breast cancer, because the clinical benefits of the dosage were demonstrated by Japanese Study E7389-J081-217 and Foreign Study E7389-G000-309. These studies used the approved dosage for the following reasons:

- Based on the results of clinical studies in patients with solid tumors and those with breast cancer, the recommended dosage of eribulin mesilate was defined in and outside Japan as follows: intravenous administration at 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 of a 3-week cycle (see the "Review Report on Halaven Injection 1 mg dated January 12, 2011"). This dosage was used in Foreign Study E7389-E044-207.
- After the start of Foreign Study E7389-E044-207, the recommended dosage was approved for breast cancer based on the results of clinical studies in patients with breast cancer treated with the recommended dosage.

PMDA accepted the applicant's explanation.

3.(ii).C.(4).2) Dose adjustment

The applicant's rationale for the dose adjustment criteria of eribulin mesilate:
Foreign Study E7389-G000-309 used dose adjustment criteria (for the start, discontinuation, and suspension of treatment with eribulin mesilate and dose reduction) that were similar to those used in Foreign Study E7389-G000-305 in patients with breast cancer. In Japanese Study E7389-J081-217, dose adjustment criteria were defined based on the criteria written in the package insert of eribulin mesilate for the approved indication. In both Foreign Study E7389-G000-309 and Japanese Study E7389-J081-217, dose adjustment according to these criteria contributed to the demonstration of the clinical benefits of eribulin mesilate. Therefore, the dose adjustment criteria for STS should be the same as for breast cancer, the approved indication.

PMDA accepted the applicant's explanation.

3.(ii).C.(4).3) Use of eribulin mesilate in combination with other antitumor drugs

No clinical study data are available on eribulin mesilate used in combination with other antitumor drugs in treating patients with unresectable STS. The applicant explained that this information would be highlighted in the "Precautions for Dosage and Administration" section of the package insert.

PMDA accepted the applicant's explanation.

3.(ii).C.(4).4) Development of eribulin mesilate for pediatric patients

PMDA asked the applicant to explain the current status of the development of a dosing regimen of eribulin mesilate for pediatric patients with unresectable STS.

The applicant's response:

Outside Japan, a phase I study is underway in pediatric patients with recurrent or refractory solid tumors (Foreign Study E7389-A001-113), initiated by the Children's Oncology Group (COG). After the completion of Foreign Study E7389-A001-113, a phase II study is scheduled to be conducted in [redacted] in accordance with [redacted].

In Japan, the applicant is paying close attention to the progress of Foreign Study E7389-A001-113, but at present has no plans to develop eribulin mesilate for pediatric patients with STS.

PMDA's view:

The applicant should gather information to explore the need for the development of eribulin mesilate for pediatric patients with STS. The applicant should also strive to promptly obtain information related to development planning of eribulin mesilate for pediatric use in and outside Japan. Then, appropriate actions should be taken to establish a dosing regimen for Japanese pediatric patients.

3.(ii).C.(5) Post-marketing investigations

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

The applicant plans to conduct post-marketing surveillance in patients with STS (hereafter, the surveillance) to evaluate the safety and other aspects of eribulin mesilate in clinical use.

In a Japanese phase II study (Japanese Study E7389-J081-217) and the post-marketing surveillance of eribulin mesilate in patients with inoperable or recurrent breast cancer (the approved indication), the following events were reported frequently and considered to be likely to have a serious outcome: bone marrow depression, infections, peripheral nerve disorder, hepatic function disorder, and interstitial lung disease. These adverse events were therefore defined as key survey items of the surveillance. In clinical pharmacology studies in patients with solid tumors, AUC and C_{max} of eribulin tended to increase in patients with hepatic or renal impairment, suggesting the need for further safety data from these patient

populations. Therefore, adverse drug reactions in patients with hepatic or renal impairment will also be included in key survey items.

The sample size of the surveillance was determined with a focus on Grade ≥3 infections. Grade ≥3 infections, a key survey item, occur frequently in association with bone marrow depression and may have a serious outcome. In Japanese Study E7389-J081-217, the lowest incidence of infection-related events (infectious pleural effusion and infection) was 2.0% (1 of 51 subjects) each. The planned sample size of the surveillance was therefore determined to be 160, which can detect Grade ≥3 infection occurring in ≥1 patient with a probability of 95%.

The applicant proposed a 2-year observation period for the surveillance, for the following reasons:

- In a Japanese phase II study (Japanese Study E7389-J081-217) and a foreign phase III study (Foreign Study E7389-G000-309), most adverse events occurred within 1 year from the start of treatment with eribulin mesilate, and no adverse events characteristically increased with increasing treatment duration. This indicates no particular long-term safety concerns. However, safety data in patients treated for ≥1 year should be collected in the surveillance, because the 2 studies have yielded only limited data regarding the safety of ≥1 year treatment.

PMDA's discussion:
The safety profile of eribulin mesilate does not clearly differ between patients with inoperable or recurrent breast cancer (the approved indication) and patients with STS [see "3.(ii).C.(2).2) Differences in the safety profile of eribulin mesilate between patients with soft tissue sarcoma and patients with breast cancer"]. The post-marketing surveillance in Japanese patients with inoperable or recurrent breast cancer has already completed; therefore, a certain amount of safety data in Japanese patients treated with eribulin mesilate are assumed available. However, because only 51 subjects were enrolled and treated with eribulin mesilate in the Japanese phase II study (Japanese Study E7389-J081-217), another post-marketing surveillance program is needed to evaluate the safety and other aspects of eribulin mesilate in patients with STS in clinical settings.

QT/QTc prolongation is an adverse event identified as requiring special attention after the initial approval. The key survey items should include QT/QTc prolongation, in addition to the events proposed by the applicant, i.e. bone marrow depression, infections, peripheral nerve disorder, hepatic function disorder, and interstitial lung disease. Data from patients with hepatic or renal impairment should be collected to understand patient characteristics. However, these patients do not need to be included in the key survey items. The proposed sample size of the surveillance is acceptable.

One-year observation period is an acceptable alternative to the proposed 2-year period, because (a) most adverse events, including those requiring special attention during treatment, were reported within 1 year from the start of treatment with eribulin mesilate, and (b) none of these adverse events increased with increasing treatment duration after 1 year from the start of treatment.

3.(iii) Adverse events, etc. observed in clinical studies

Adverse event data are included in the clinical study results submitted for safety evaluation. Major adverse events other than death are summarized in "3.(iii).(1)" to 3.(iii).(3)." Death data are presented in "3.(ii) Summary of clinical efficacy and safety."

3.(iii).(1) Japanese phase II study (Japanese Study E7389-J081-217)

All subjects experienced adverse events. All subjects also experienced adverse events for which a causal relationship with eribulin mesilate could not be ruled out. The adverse events occurring at an incidence of ≥20% are shown in the table below.

Adverse events with an incidence of ≥20%

System Organ Class Preferred Term (MedDRA/J ver.17.1)	n (%) N = 51	
	All Grades	Grade ≥3
All adverse events	51 (100)	49 (96.1)
Blood and lymphatic system disorders		
Anaemia	24 (47.1)	7 (13.7)
Leukopenia	51 (100)	38 (74.5)
Lymphopenia	40 (78.4)	17 (33.3)
Neutropenia	50 (98.0)	44 (86.3)
Gastrointestinal disorders		
Constipation	16 (31.4)	0
Nausea	21 (41.2)	0
Stomatitis	13 (25.5)	0
General disorders and administration site conditions		
Malaise	20 (39.2)	0
Pyrexia	21 (41.2)	1 (2.0)
Infections and infestations		
Nasopharyngitis	11 (21.6)	0
Upper respiratory tract infection	11 (21.6)	0
Investigations		
Alanine aminotransferase increased	14 (27.5)	3 (5.9)
Aspartate aminotransferase increased	13 (25.5)	2 (3.9)
Blood lactate dehydrogenase increased	11 (21.6)	0
Metabolism and nutrition disorders		
Decreased appetite	12 (23.5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Cancer pain	23 (45.1)	3 (5.9)
Nervous system disorders		
Dysgeusia	12 (23.5)	0
Neuropathy peripheral	16 (31.4)	0
Skin and subcutaneous tissue disorders		
Alopecia	14 (27.5)	0

The following serious adverse events occurred in 15 of 51 subjects (29.4%): cancer pain in 3 subjects (5.9%), ileus in 2 subjects (3.9%), and febrile neutropenia, cardiac failure, cataract, hepatic haemorrhage, infectious pleural effusion, pneumonia, *Streptococcal* infection, tumour embolism, tumour haemorrhage, hydronephrosis, dyspnoea, and pulmonary embolism in 1 subject (2.0%) each. A causal relationship to eribulin mesilate could not be ruled out for febrile neutropenia, hepatic haemorrhage, infectious pleural effusion, *Streptococcal* infection, tumour haemorrhage, and pulmonary embolism in 1 subject each.

The following adverse events led to the discontinuation of eribulin mesilate in 4 of 51 subjects (7.8%): cardiac failure, infectious pleural effusion, pneumonia, and interstitial lung disease in 1 subject (2.0%) each. A causal relationship to eribulin mesilate could not be ruled out for infectious pleural effusion and interstitial lung disease in 1 subject each.

3.(iii).(2) Foreign phase II study (Foreign Study E7389-E044-207)

Adverse events occurred in 124 of 127 subjects (97.6%), and those for which a causal relationship with eribulin mesilate could not be ruled out were observed in 114 of 127 subjects (89.8%). The adverse events occurring at an incidence of ≥20% are shown in the table below.

Adverse events with an incidence of ≥20%

System Organ Class Preferred Term (MedDRA/J ver.15.0)	n (%) N = 127	
	All Grades	Grade ≥3
All adverse events	124 (97.6)	66 (52.0)
Gastrointestinal disorders		
Abdominal pain	29 (22.8)	1 (0.8)
Constipation	34 (26.8)	2 (1.6)
Diarrhoea	30 (23.6)	1 (0.8)
Nausea	45 (35.4)	1 (0.8)
Vomiting	26 (20.5)	3 (2.4)
General disorders and administration site conditions		
Fatigue	89 (70.1)	14 (11.0)
Pyrexia	27 (21.3)	2 (1.6)
Investigations		
Weight decreased	34 (26.8)	1 (0.8)
Metabolism and nutrition disorders		
Decreased appetite	39 (30.7)	1 (0.8)
Musculoskeletal and connective tissue disorders		
Myalgia	26 (20.5)	2 (1.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour pain	48 (37.8)	9 (7.1)
Nervous system disorders		
Dizziness	27 (21.3)	1 (0.8)
Peripheral sensory neuropathy	46 (36.2)	4 (3.1)
Respiratory, thoracic and mediastinal disorders		
Cough	30 (23.6)	1 (0.8)
Dyspnoea	41 (32.3)	6 (4.7)
Skin and subcutaneous tissue disorders		
Alopecia	61 (48.0)	0

Serious adverse events occurred in 47 of 127 subjects (37.0%). The serious adverse events reported in ≥2 subjects were general physical health deterioration, pyrexia, febrile neutropenia, and tumour pain in 4 subjects (3.1%) each, pneumonia and dyspnoea in 3 subjects (2.4%) each, and neutropenia, cerebral ischaemia, confusional state, pulmonary embolism, and catheter site infection in 2 subjects (1.6%) each. A causal relationship to eribulin mesilate could not be ruled out for febrile neutropenia in 4 subjects, neutropenia, pyrexia, and pneumonia in 2 subjects each, and cerebral ischaemia and dyspnoea in 1 subject each.

Adverse events led to the discontinuation of eribulin mesilate* in 11 of 127 subjects (8.7%). Detailed information on the adverse events leading to the discontinuation of eribulin mesilate was not collected.

* The figure (11 subjects) represent the number of subjects who discontinued treatment primarily due to an adverse event.

3.(iii).(3) Foreign phase III study (Foreign Study E7389-G000-309)

Adverse events occurred in 224 of 226 subjects (99.1%) in the eribulin mesilate group and 218 of 224 subjects (97.3%) in the DTIC group. Adverse events for which a causal relationship to study drug could not be ruled out were observed in 210 of 226 subjects (92.9%) in the eribulin mesilate group and 203 of 224 subjects (90.6%) in the DTIC group. The adverse events occurring at an incidence of ≥20% in either group are shown in the table below.

Adverse events with an incidence of ≥20% in either group

System Organ Class Preferred Term (MedDRA/J ver.17.1)	n (%)			
	Eribulin mesilate N = 226		DTIC N = 224	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	224 (99.1)	152 (67.3)	218 (97.3)	126 (56.3)
Blood and lymphatic system disorders				
Neutropenia	99 (43.8)	80 (35.4)	53 (23.7)	35 (15.6)
Anaemia	67 (29.6)	16 (7.1)	69 (30.8)	27 (12.1)
Thrombocytopenia	13 (5.8)	1 (0.4)	62 (27.7)	34 (15.2)
Gastrointestinal disorders				
Constipation	71 (31.4)	2 (0.9)	58 (25.9)	1 (0.4)
Nausea	91 (40.3)	2 (0.9)	106 (47.3)	1 (0.4)
Vomiting	43 (19.0)	2 (0.9)	50 (22.3)	1 (0.4)
General disorders and administration site conditions				
Fatigue	99 (43.8)	7 (3.1)	86 (38.4)	3 (1.3)
Asthenia	47 (20.8)	4 (1.8)	51 (22.8)	7 (3.1)
Pyrexia	63 (27.9)	2 (0.9)	31 (13.8)	1 (0.4)
Nervous system disorders				
Peripheral sensory neuropathy	46 (20.4)	4 (1.8)	8 (3.6)	0
Skin and subcutaneous tissue disorders				
Alopecia	79 (35.0)	1 (0.4)	6 (2.7)	0

Serious adverse events occurred in 76 of 226 subjects (33.6%) in the eribulin mesilate group and 71 of 224 subjects (31.7%) in the DTIC group. The following serious adverse events occurred in ≥2 subjects receiving eribulin mesilate: neutropenia in 11 subjects (4.9%), pyrexia in 10 subjects (4.4%), anaemia in 5 subjects (2.2%), abdominal pain, intestinal obstruction, urinary tract infection, pulmonary embolism, and respiratory failure in 4 subjects (1.8%) each, leukopenia, asthenia, and pneumonia in 3 subjects (1.3%) each, and febrile neutropenia, diarrhoea, small intestinal obstruction, general physical health deterioration, hyperbilirubinaemia, lung infection, peritonitis bacterial, back pain, pathological fracture, cancer pain, and dyspnoea in 2 subjects (0.9%) each. The following serious adverse events occurred in ≥2 subjects receiving DTIC: thrombocytopenia in 13 subjects (5.8%), neutropenia in 10 subjects (4.5%), anaemia in 9 subjects (4.0%), intestinal obstruction in 5 subjects (2.2%), abdominal pain, pyrexia, and dyspnoea in 4 subjects (1.8%) each, leukopenia, pancytopenia, small intestinal obstruction, and deep vein thrombosis in 3 subjects (1.3%) each, and febrile neutropenia, diarrhoea, pneumonia, haemoglobin decreased, malignant pleural effusion, respiratory failure, pleural effusion, and

hypotension in 2 subjects (0.9%) each. A causal relationship with the study drug could not be ruled out for the following events: neutropenia in 11 subjects, anaemia and pyrexia in 4 subjects each, leukopenia in 3 subjects, febrile neutropenia and asthenia in 2 subjects each, and intestinal obstruction, diarrhoea, and pneumonia in 1 subject each in the eribulin mesilate group; and thrombocytopenia in 13 subjects, neutropenia in 10 subjects, anaemia in 7 subjects, leukopenia in 3 subjects, febrile neutropenia, pancytopenia, pyrexia, and pneumonia in 2 subjects each, and diarrhoea, haemoglobin decreased, dyspnoea, and hypotension in 1 subject each in the DTIC group.

Adverse events led to the discontinuation of study drug in 17 of 226 subjects (7.5%) in the eribulin mesilate group and 11 of 224 subjects (4.9%) in the DTIC group. Adverse events leading to the discontinuation of study drug occurring in ≥2 subjects in either group were thrombocytopenia and fatigue in 2 subjects (0.9%) each in the eribulin mesilate group and thrombocytopenia in 3 subjects (1.3%) and fatigue in 2 subjects (0.9%) in the DTIC group. A causal relationship with the study drug could not be ruled out for all events.

III. Results of 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

The new drug application data were subjected to a document-based compliance inspection and data integrity assessment, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no particular problems. PMDA thus concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

The new drug application data (5.3.5.2.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed no particular problems. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of eribulin mesilate in the treatment of soft tissue sarcoma has been demonstrated and its safety is acceptable in view of its observed benefits. Eribulin mesilate has clinical value as a new therapeutic option for soft tissue sarcoma. The efficacy and clinical positioning of eribulin mesilate, post-marketing investigations, etc. will be further discussed at the Expert Discussion.

This application may be approved if eribulin mesilate is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

January 8, 2016

I. Product Submitted for Registration

[Brand name]	Halaven Injection 1 mg
[Non-proprietary name]	Eribulin Mesilate
[Applicant]	Eisai Co., Ltd.
[Date of application]	July 30, 2015

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 Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

PMDA's conclusion after discussion [for discussion summary, see "3.(ii).C.(1) Efficacy" of Review Report (1)]:

In a foreign phase III study conducted in patients with STS (Study E7389-G000-309), overall survival, the primary endpoint, was significantly longer in the eribulin mesilate group than in the dacarbazine group, the control group. The efficacy of eribulin mesilate in patients with soft tissue sarcoma (STS) has thus been demonstrated.

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

(2) Safety

PMDA's conclusion after discussion [for discussion summary, see "3.(ii).C.(2) Safety" of Review Report (1)]:

At the initial approval of eribulin mesilate, bone marrow depression, peripheral nerve disorder, infections, hepatic function disorder, and interstitial lung disease were identified as requiring special attention during eribulin mesilate therapy in patients with breast cancer. In patients with STS receiving eribulin mesilate, special attention should be paid to QT/QTc prolongation as well as these events. Nevertheless, eribulin mesilate is tolerable in patients with STS as long as they are followed appropriately by a physician with sufficient knowledge and experience in cancer chemotherapy through monitoring and controlling adverse events, dose reduction, or the suspension or discontinuation of treatment.

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

(3) Clinical positioning and indications

PMDA's conclusion after discussion [for discussion summary, see "3.(ii).C.(3) Clinical positioning and indications" of Review Report (1)]:

Eribulin mesilate is a therapeutic option for patients with unresectable STS who have received chemotherapy with doxorubicin hydrochloride or other agents. The indication should be "soft tissue sarcoma" as proposed by the applicant. The "Clinical Studies" section of package insert should provide information such as histological types of STS of patients enrolled in the clinical studies, and the "Precautions for Indication" section should have the following precautionary advice:

- The efficacy and safety of eribulin mesilate in chemotherapy-naïve patients have not been established.
- Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, including histological types of STS in patients enrolled in the clinical studies, and based on adequate knowledge of the efficacy and safety of eribulin mesilate.

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

PMDA advised the applicant to ensure that the above statements are included in the "Indications" and "Precautions for Indications" sections of the package insert. The applicant agreed.

(4) Dosage and administration

PMDA's conclusion after discussion [for discussion summary, see "3.(ii).C.(4) Dosage and administration" of Review Report (1)]:

As proposed by the applicant, the dosage and administration of eribulin mesilate 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 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." The precautionary advice in the "Precautions for Dosage and Administration" section for the approved indication should also be used for the additional indication.

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

(5) Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance in patients with STS receiving eribulin mesilate (hereafter, the surveillance) to gather data on the safety and other aspects of eribulin mesilate in clinical use (planned sample size, 160; observation period, 2 years). Key survey items for the surveillance will include bone marrow depression, infections, peripheral nerve disorder, hepatic function disorder, interstitial lung disease, and adverse drug reactions in patients with hepatic or renal impairment.

PMDA's conclusion after discussion [for discussion summary, see "3.(ii).C.(5) Post-marketing investigations" of Review Report (1)]:
Post-marketing surveillance should be conducted to evaluate the safety and other aspects of eribulin mesilate in clinical use in patients with STS in Japan, because only 51 subjects were enrolled and treated with eribulin mesilate in a Japanese phase II study (Japanese Study E7389-J081-217). The following may be considered in the design of the surveillance:

- QT/QTc prolongation was identified as an attention-requiring adverse event after the initial approval. Key survey items should therefore include QT/QTc prolongation in addition to the following events selected by the applicant: bone marrow depression, infections, peripheral nerve disorder, hepatic function disorder, and interstitial lung disease. There is little need to include patients with hepatic or renal impairment in the key survey items.
- The proposed target sample size of the surveillance is acceptable.
- One-year observation period is an acceptable alternative to the proposed 2-year observation period.

In the Expert Discussion, expert advisors supported the PMDA's view, noting that the appropriate observation period of the surveillance would be 1 year in light of the frequency of adverse events in the clinical studies both in and outside Japan.

Accordingly, PMDA advised the applicant to reconsider the post-marketing surveillance plan. The applicant noted that they would re-design the surveillance with optimum survey items so that necessary safety information is gathered efficiently. The applicant made the following comments:

- Bone marrow depression, infections, peripheral nerve disorder, hepatic function disorder, interstitial lung disease, and QT/QTc prolongation will be defined as key survey items.
- In light of the frequency of adverse events in the Japanese or foreign clinical studies, the observation period of surveillance will be set as 1 year.

PMDA accepted the applicant's comments on the surveillance plan (draft).

In view of the discussion above, PMDA has concluded that the risk management plan (draft) should include the safety and efficacy specifications, additional pharmacovigilance activities, and risk minimization activities presented in the tables below.

Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Bone marrow depression • Infections • Peripheral nerve disorder • Hepatic function disorder • Interstitial lung disease • Use in patients with hepatic impairment	• QT/QTc prolongation • Testicular toxicity	None
Efficacy specification		
• Efficacy in clinical use (soft tissue sarcoma)		

Summary of additional pharmacovigilance activities and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (soft tissue sarcoma) [For the outline of the plan (draft), see the table below.] • Specified use-results survey (survey on the occurrences and causal factors of peripheral nerve disorder in patients with inoperable or recurrent breast cancer)	• Disseminate information gathered from early post-marketing phase vigilance. • Prepare and distribute information materials for healthcare professionals.

Underlines denote activities for the additional indication.

Outline of specified use-results survey (draft)

Objective	To review the safety and other aspects of eribulin mesilate in clinical use
Survey method	Central registration system
Population	Patients with soft tissue sarcoma treated with eribulin mesilate
Observation period	1 year
Planned sample size	160 patients
Main survey item(s)	Key survey items: bone marrow depression, infections, peripheral nerve disorder, hepatic function disorder, interstitial lung disease, and QT/QTc prolongation Other main survey items: patient characteristics (including histological types of STS), prior treatment of the primary disease, exposure to eribulin mesilate, concomitant drugs and therapies, adverse events (including abnormal changes in laboratory values), etc.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration with the condition written below, given that the package insert will provide precautionary advice and information concerning the proper use of the product to healthcare professionals appropriately after market launch. The product should be used under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy at a medical center well-prepared for emergencies. The product has been designated as an orphan drug, and is expected to be indicated for soft tissue sarcoma. Therefore, the appropriate re-examination period for the additional indication should be 10 years.

[Indications]

Inoperable or recurrent breast cancer and soft tissue sarcoma

(Underline denotes addition.)

[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.

(No changes)

[Condition for Approval]

The applicant is required to develop and appropriately implement a risk management plan.

[Warnings] (No changes)

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] (No changes)

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 Indications] (Underlines denote addition.)

1. Inoperable or recurrent breast cancer
   (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.
2. Soft tissue sarcoma
   (1) The efficacy and safety of eribulin mesilate in chemotherapy-naïve patients have not been established.
   (2) Eligible patients must be selected based on a careful review of the content of the "Clinical Studies" section, including histological types of STS in patients enrolled in the clinical studies, and based on adequate knowledge of the efficacy and safety of eribulin mesilate.

[Precautions for Dosage and Administration] (Word struck through is deleted.)

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.